The New England
Journal of Medicine

Copyright, 1956, by the Massachusetts Medical Society

Volume 254 JANUARY 26, 1956 Number 4

MANAGEMENT OF PATIENTS WITH PORTAL HYPERTENSION UNDERGOING VENOUS-SHUNT SURGERY*

W. Carl Ebeling, M.D.,† John P. Bunker, M.D.,‡ Daniel S. Ellis, M.D.,§ Arthur B. French, M.D.,¶ Robert R. Linton, M.D.,‖ and Chester M. Jones, M.D.**

BOSTON

THE dangers of surgery in patients with liver disease have long been recognized but poorly understood. With the recent development of venous-shunt surgery for the relief of portal hypertension a relatively large group of such patients have become available for study. This report represents ten years' experience with 129 patients undergoing 140 anastomoses and attempted anastomoses between the portal and systemic venous systems. Correlation of preoperative clinical and laboratory findings with operative and immediate postoperative events has provided prognostic criteria for the selection and management of this particular group of patients — and for the management of any patient with chronic liver disease undergoing major surgery.

Clinical Material and Methods

The majority of the 129 patients had well marked, chronic, parenchymal liver disease, and all but 6 had suffered previous massive hemorrhage from esophageal varices. There were 104 operations on 100 patients with cirrhosis and intrahepatic portal-bed block, and 36 operations on 29 patients with extrahepatic portal obstruction and no gross or microscopical evidence of liver disease. All but 1 of these patients had a liver biopsy either before or at the time of the operative procedure. The histologic diagnoses on the abnormal livers included portal cirrhosis, alcoholic type; portal cirrhosis, postnecrotic type; portal cirrhosis with nonspecific granulomatous lesions; biliary cirrhosis; and sarcoidosis. It is of interest that in 55 per cent of this entire group, no history of excessive alcoholic intake was obtainable.

The bromsulfalein retention (5 mg. per kilogram of body weight in forty-five minutes), serum albumin and globulin, serum bilirubin, cephalin-cholesterol flocculation, serum alkaline phosphatase and one-stage (Quick) prothrombin time were determined. The chemical methods used were the same as in previous reports.[1,2] In most cases many of the liver-function tests were repeated after operation before the patient left the hospital, and in a group of 37 consecutive patients, the complete battery of function tests were repeated on the first, third, fifth and tenth postoperative days.[1]

On the basis of the preoperative liver-function tests alone, we have found that it is not always possible to delineate sharply between cases of cirrhosis (with intrahepatic obstruction) and cases of extrahepatic obstruction. In several patients with negative liver-function tests liver biopsy disclosed marked portal cirrhosis. Conversely, a few patients with distinctly abnormal liver function on the tests have had livers that a single biopsy and gross inspection at the time of operation showed to be normal. Therefore, because of our inability consistently to fit these patients into sharply defined etiologic and anatomic classifications, we have divided the cases of portal hypertension on the basis of function into arbitrary groups of "mild," "moderate" and "severe" liver dysfunction, as well as into anatomic groups of intrahepatic and extrahepatic portal-bed block. By arbitrary definition the "mild" cases showed a bromsulfalein retention of 10 per cent or less at some time in the period of preoperative study; they included most of the patients with extrahepatic portal-bed block (usually thrombosis of the splenic or portal vein, commonly called Banti's syndrome) as well as a few with well compensated cirrhosis. In the "moderate" and "severe" cases bromsulfalein retention was always more than 10 per cent. Whereas the patients with "moderate" liver disease had serum albumin levels of 3 gm. per 100 ml. or higher just be-

*From the Anesthesia Laboratory and the Department of Medicine, Harvard Medical School and Massachusetts General Hospital.

Supported through the generosity of Mr. Edward Mallinckrodt.

†Assistant professor of medicine, University of Maryland School of Medicine, Baltimore; visiting physician, University Hospital, Baltimore.

‡Assistant clinical professor of anesthesia, Harvard Medical School; associate anesthetist, Massachusetts General Hospital.

§Assistant in medicine, Harvard Medical School; assistant physician, Massachusetts General Hospital.

¶Associate professor of medicine, Wayne University College of Medicine, Detroit.

‖Assistant clinical professor of surgery, Harvard Medical School; visiting surgeon, Massachusetts General Hospital.

**Clinical professor of medicine, Harvard Medical School; consulting visiting physician, Massachusetts General Hospital.

fore operation, those with "severe" liver disease, by definition, had levels below 3 gm. per 100 ml. Cases in which intravenous albumin therapy was required to achieve levels above 3 gm. per 100 ml. were classified as "severe." Except for this single modification, this is the same classification used by French et al.[1]

Preoperative Preparation

As a rule, each of these patients was seen at the time of admission by the surgeon and by an internist, who together prepared the patient, chose the time of operation and informed the anesthetist and the blood-bank personnel of the special problems involved. The evaluation and therapy of these patients before operation was usually a day-to-day process constantly subject to change. The major problem in evaluation was to determine the degree of liver dysfunction and the degree of activity of liver disease. If there were signs of active intrahepatic disease or decompensation, such as liver tenderness, fever, jaundice, edema or ascites, marked malnutrition or impairment of mental status, or if the liver biopsy showed active necrosis of liver cells or infiltration with polymorphonuclear leukocytes, operation was postponed for weeks or even months of medical preparation.

On the other hand, if there were no signs of currently active liver disease, the evaluation may have shown a state of liver dysfunction that could be expected to improve little by further medical therapy. The problem was then one of adjusting the patient's nutrition and estimating the risk of operation against the risk of renewed bleeding.

Some patients who were admitted to the hospital after an episode of brisk hemorrhage or slow, long-continued oozing from esophageal varices, had clinical and laboratory signs that suggested a very advanced stage of liver disease. A major hemorrhage occasionally precipitated fatal or nearly fatal liver failure with hypoalbuminemia, jaundice and ascites that persisted for a long time. This occasional situation indicated a grave prognosis. But if these patients were handled thoughtfully and firmly and with persistent attention to all details of supportive therapy, they often improved to a point where they could withstand the major impact of shunt surgery.

The preoperative therapy of these patients consisted in general of the institution of an adequate diet, the limitation of physical activity and correction of any deficits in the hemoglobin and serum albumin levels. The diet included generous intakes of soft, easily digested foods in small, frequent feedings, rich in carbohydrates, adequate in proteins and often low in sodium content, and supplemented with some adequate form of vitamin B complex and vitamin K. These patients were usually confined to bed except for short periods up and around the ward and bathroom privileges daily. Anemia was corrected by the judicious use of transfusions until the patient's hemoglobin rose to a level of 12 gm. per 100 ml. or higher. In most cases serum albumin levels rose to 3 gm. per 100 ml. or higher on the program of dietary treatment supplemented with transfusions described above. Occasionally, however, it was necessary to give salt-free human albumin intravenously to raise the serum albumin level above 3 gm. per 100 ml.

All the operations under study were venous shunts (or attempted shunts) designed to reduce portal pressure. They were end-to-side splenorenal anastomoses, end-to-side portacaval anastomoses, side-to-side portacaval anastomoses, make-shift anastomoses (such as superior mesenteric vein to inferior vena cava, inferior mesenteric vein to left adrenal vein and inferior mesenteric vein to left ovarian vein), and finally operations at which no successful anastomosis could be completed. All operations were performed by the same surgeon (R.R.L.).

The principal anesthetic agents used were ether, cyclopropane and spinal procaine or tetracaine. Sixty-two operations were done under ether, 36 under cyclopropane, and 41 under spinal anesthesia. Thirty-two of these were hypotensive spinal, and 9 were normotensive spinal. A single operation was done under thiopental (Pentothal) sodium, nitrous oxide and succinylcholine when the spinal technic failed.

Postoperative Management

Constant expert nursing care was provided for at least the first sixty hours after operation. Routine orders included nasal administration of oxygen for twenty-four to forty-eight hours, at a rate of 6 to 7 liters per minute, in an attempt to minimize the possibility of anoxia and any additional insult to the liver. Most patients received a minimum of 250 gm. of glucose daily by vein (as 10 or 25 per cent solution in water) until they were able to take this much orally. A review of patients who had liver failure made it clear that many of them did not get what we now consider adequate glucose intravenously. By the third or fourth day most of them could begin to handle oral feedings, and their diets were gradually stepped up as tolerated over the next ten-day period. (This should not be pushed too rapidly, but every effort should be made to get in an adequate caloric intake by means of intravenous supplements as long as needed.) In patients with signs of liver failure with ammonia intoxication, the protein intake was limited to 40 to 60 gm. a day, the carbohydrate intake increased to 300 gm. or more, and in recent cases L-glutamic acid was given by mouth or sodium glutamate intravenously in an attempt to reduce the blood ammonia level.[3] Intravenous and oral feedings were supplemented by therapeutic doses of vitamins C, K and the B complex. When necessary, transfusions were used in the immediate postoperative period to maintain a hemoglobin of 12 gm. per 100 ml.

We usually started activity by allowing the patients to dangle their legs on the fourth postoperative day, and thereafter ambulation was increased gradually, with care not to permit undue fatigue or exhaustion. Those with more severely damaged livers were, of course, brought along more slowly and more cautiously. All patients were seen twice a day by physicians thoroughly experienced in dealing with this type of disease and by those who were alert to the complications that may rapidly and often insidiously arise. In the absence of complications the patient was usually ready for discharge at the end of two weeks to continue convalescence at home.

Clinical Classifications

We have grouped the immediate surgical results of each operation as follows: uncomplicated recovery; nonfatal complications unrelated to primary liver disease (such as infection, atelectasis, thrombophlebitis, hematemesis and temperature of 102°F. or above for longer than forty-eight hours); nonfatal liver failure, manifested by appearance of ascites, peripheral edema, undue somnolence, tenderness of the liver with increasing jaundice and frank hepatic coma; liver death from hepatic failure; hemorrhagic death from uncontrollable bleeding in the operative field; and death from other causes such as postoperative hematemesis and infection. The immediate postoperative results, based on these classifications, were correlated with relevant historical facts, preoperative physical findings, laboratory data and operative data (Tables 1-6).

TABLE 2. *Age Distribution of Patients.*

	Age	Operations	Hemorrhagic Deaths	Liver Deaths	Deaths from Other Causes	Cases of Nonfatal Liver Failure
	yr.					
Patients with cirrhosis:	6-29	7	—	—	—	—
	30-39	20	—	2	—	3
	40-49	36	3	—	2	3
	50-59	22	1	3	—	5
	60-	19	—	3	2	2
	Totals	104	4	8	4	13
Patients with extrahepatic block:	6-29	21	—	—	—	—
	30-39	4	—	—	—	—
	40-49	3	—	—	—	1
	50-59	6	1	—	—	—
	60-	2	—	—	—	—
	Totals	36	1	0	0	1

Results and Discussion

Over-All Results

The over-all results are summarized in Table 1. Seventy-one of the 140 shunts and attempted shunts were followed by an entirely uneventful postoperative recovery. Thirty-eight operations were followed by

TABLE 1. *Over-All Results — Correlation with Type of Liver Disease.*

Classification	Period	Operations	Hemorrhagic Deaths	Liver Deaths	Deaths from Other Causes	Cases of Nonfatal Liver Failure	Other Complications	Cases of Uneventful Recovery
Anatomic:								
Cirrhosis & intrahepatic portal-bed block	1945-1949	28	4	2	3	1	12	6
	1950-1954	76	—	6	1	12	17	40
Extrahepatic portal-bed block	1945-1949	21	1	—	—	1	4	15
	1950-1954	15	—	—	—	—	5	10
Totals		140	5	8	4	14	38	71
Functional:								
Mild liver disease	1945-1949	22	—	—	1	1	8	12
	1950-1954	21	—	—	1	—	3	17
Moderate liver disease	1945-1949	23	4	—	2	1	7	9
	1950-1954	65	—	5	—	10	18	32
Severe liver disease	1945-1949	4	1	2	—	—	1	—
	1950-1954	5	—	1	—	2	1	1
Totals		140	5	8	4	14	38	71

serious but nonfatal complications commonly seen after other types of major surgery (atelectasis, thrombophlebitis, wound sepsis and so forth). Four patients died from postoperative complications that were not directly related to the liver.

Complications or deaths during and after the remaining 27 operations were directly related to the liver and represent the serious hazards peculiar to major surgery in this class of patients. Frank liver failure developed in 22 patients, of whom 8 died and 14 recovered, and 5 patients died during surgery of massive, uncontrollable hemorrhage.

TABLE 3. *Correlation of Laboratory Tests with Postoperative Course.*

TEST & RESULT	OPERATIONS	HEMORRHAGIC DEATHS	LIVER DEATHS	DEATHS FROM OTHER CAUSES	CASES OF NONFATAL LIVER FAILURE
Serum albumin:					
4.0 gm./100 ml. or more	70	3	1	3	4
3.5-3.9 gm./100 ml.	42	1	3	—	5
3.0-3.4 gm./100 ml.	21	1	1	1	4
2.9 gm./100 ml. or less	6	—	3	—	1
Totals	139	5	8	4	14
Bromsulfalein retention*:					
0-10 mg.	41	—	—	2	1
11-20 mg.	39	1	2	2	4
21-30 mg.	27	2	2	—	5
31-40 mg.	22	1	4	—	2
41 mg. or over	5	1	—	—	—
Totals	134	5	8	4	12
Cephalin-cholesterol flocculation†:					
0 or +	24	—	—	—	1
++	35	—	1	1	3
+++	50	3	2	2	7
++++	24	2	4	1	3
Totals	133	5	7	4	14
Serum bilirubin:					
0.7 mg./100 ml. or less	34	1	—	1	3
0.8-1.9 mg./100 ml.	65	—	4	3	7
2.0 mg./100 ml. or more	25	3	2	—	3
Totals	124	4	6	4	13
Prothrombin time: (137 operations)					
76-100%	56	—	1	2	6
50-75%	70	4	4	2	7
Below 50%	11	1	2	—	1
Totals	137	5	7	4	14
Alkaline phosphatase:					
0-4.0 Bodansky units	31	—	1	2	4
4.1-10 Bodansky units	43	—	3	—	3
10.1 Bodansky units or more	27	1	1	—	4
Totals	101	1	5	2	11

*5 mg./kg. of body weight in 45 min.
†In 48 hr.

Liver failure was manifested by the development of ascites and edema, drowsiness, confusion and a coarse, flapping tremor. Increased liver tenderness and fever were particularly common. The diffusible blood ammonia, measured in the more recent cases, was elevated. Clinical jaundice usually appeared or increased in these patients, but the presence of postoperative jaundice alone was not considered to represent liver failure.

TABLE 4. *Correlation of Physical Factors with Postoperative Course.*

PHYSICAL FACTOR	FINDING ON PHYSICAL EXAMINATION	OPERATIONS	HEMORRHAGIC DEATHS	LIVER DEATHS	DEATHS FROM OTHER CAUSES	CASES OF NONFATAL LIVER FAILURE
Spider angiomas	Present	54	2	6	1	8
	Absent	86	3	2	3	6
Jaundice	Present	24	3	2	—	5
	Absent	116	2	6	4	9
Purpura	Present	8	1	1	—	1
	Absent	131	4	7	4	13
Ascites	Present	28*	3	3	1	2
	Absent	108	2	4	3	12
Liver	Palpable	98	5	8	3	12
	Nonpalpable	42	—	—	1	2
Cirrhotic liver (104 operations)	Palpable	80	4	8	3	12
	Nonpalpable	24	—	—	1	1
Extra hepatic block (36 operations)	Palpable	18	1	—	—	—
	Nonpalpable	18	—	—	—	1

*In four patients presence or absence of ascites equivocal, with no clear statement in medical record.

TABLE 5. *Correlation of Type of Shunt with Postoperative Course.*

SHUNT	DEGREE OF LIVER DYSFUNCTION	OPERATIONS	HEMORRHAGIC DEATHS	LIVER DEATHS	DEATHS FROM OTHER CAUSES	CASES OF NONFATAL LIVER FAILURE
Splenorenal	Mild	19	—	—	2	1
	Moderate	58	2	2	1	5
	Severe	6	1	1	—	1
Totals		83	3	3	3	7
Portacaval	Mild	9	—	—	—	—
	Moderate	24	—	3	—	6
	Severe	3	—	2	—	1
Totals		36	—	5	—	7
Attempted only	Mild	11	—	—	—	—
	Moderate	5	2	—	—	—
	Severe	—	—	—	—	—
Totals		16	2	—	—	—
Makeshift	Mild	4	—	—	—	—
	Moderate	1	—	—	1	—
	Severe	—	—	—	—	—
Totals		5	—	—	1	—

Five patients died of uncontrollable bleeding from the venous and capillary bed in the operative field. All 5 were among the first 49 operations (1945-1949). Fresh blood for transfusion became available in this hospital in 1949, and with the use of fresh

blood for the replacement of operative blood loss in patients with liver disease, uncontrollable bleeding during shunt surgery has practically disappeared. More recently the introduction of hypotensive spinal anesthesia (as pointed out below) has further decreased the difficulties of surgical bleeding.

Mortality

The most striking single feature of the data is the progressive decrease in mortality. At the end of 1949, 49 operations had been performed, with 10 deaths — a mortality of 20.4 per cent. In the period 1950 through 1954, 91 operations were performed, with 7 deaths, giving a mortality of 7.7 per cent and an over-all operative mortality for the entire ten-year period of 12.1 per cent. As the mortality fell, there was a simultaneous increase in the proportion of patients with more serious degrees of liver disease who were accepted for surgery. In the 1945-1949 period, 27 of the 49 operations (55 per cent) were performed on patients with "moderate" or "severe" liver disease, whereas in the period 1950-1954, 70 out of the 91 operations (78 per cent) were done on patients with "moderate" or "severe" liver disease, the groups that, as stated below, have provided virtually all the serious complications.

The improvement in results, including successful surgery in the presence of increasing degrees of preoperative liver damage, must be attributed to improving surgical, medical, anesthetic and blood-bank technics, and to an increasing awareness of the many factors, outlined in the following section, that contribute to the success or failure of shunt surgery.

Correlation of Results with Anatomic Diagnosis

It was to be expected that postoperative liver failure would be more frequent in patients with frank liver disease recognizable preoperatively. The data support this expectation impressively (Table 1). There were 21 cases of postoperative liver failure (of which 8 were fatal) and 4 deaths from uncontrollable hemorrhage in the group of 104 operations on patients with cirrhosis or intrahepatic portal-bed block. In contrast, there was but a single case of postoperative liver failure and a single "hemorrhagic death" among 36 operations in patients with extrahepatic portal-bed block.

Thus, the presence or absence of intrahepatic disease is of great prognostic value. But it is not always possible to make or exclude the diagnosis of cirrhosis on the basis of history, physical examination or liver-function tests. In many cases the final diagnosis (as summarized in the upper portion of Table 1) was made on the basis of the operative biopsy. Fortunately, a functional classification of patients, based on preoperative liver-function tests, has proved to be at least as valuable a prognostic guide (lower portion of Table 1). In many of the early cases in this series we obtained preoperative aspiration liver biopsies with the needle technic. We have subsequently come to believe that in most cases this is an unnecessary procedure and now rely primarily on clinical and laboratory examinations.

Laboratory Examinations

Serum albumin. A low serum albumin gave an almost uniformly poor prognosis. The serum albumin was below 3.0 gm. per 100 ml. at the time of surgery in 6 patients; 3 of the 6 died of postoperative liver failure, and a fourth suffered liver failure but recovered. In 4 other patients a low preoperative serum albumin was raised to above 3.0 gm. per 100 ml. by means of human albumin administered by vein. One of the 4 died of uncontrollable operative hemorrhage, and a second suffered nonfatal postoperative liver failure. Nine of these 10 patients comprise the group designated above as "severe liver disease"; the tenth, who did well postoperatively, had less than 10 per cent bromsulfalein retention, thus qualifying as having "mild liver disease."

Table 6. *Correlation of Anesthetic Agent with Postoperative Course.*

Anesthetic*	Operations	Hemorrhagic Deaths	Liver Deaths	Deaths from Other Causes	Cases of Nonfatal Liver Failure
Ether	62	3	4	2	7
Cyclopropane	36	2	1	1	4
Hypotensive spinal	32	—	3	1	2
Normotensive spinal	9	—	—	—	1
Pentothal, nitrous oxide & succinylcholine	1	—	—	—	—

*Relative numbers of portacaval & splenorenal shunts & of patients with "mild," "moderate" & "severe" liver disease approximately same for ether, cyclopropane & hypotensive spinal anesthesia.

It should be mentioned that 3 of the 9 patients with severe liver disease were operated on while actively bleeding — the only "emergency" shunts in the entire series. If these 3 patients are excluded, the outcome for the remaining 6 operations in the presence of "severe" liver disease is just as poor: four of the 6 suffered liver failure, "liver death" or "hemorrhagic death."

Although a low serum albumin is of grave prognostic significance, a high serum albumin did not guarantee against postoperative liver failure. After 70 operations on patients with a serum albumin of 4.0 gm. per 100 ml. or above, "hemorrhagic death" occurred in 3, fatal liver failure in 1, and nonfatal liver failure in 4 cases.

Bromsulfalein retention. Patients classified as having "mild liver disease" — preoperative bromsulfalein retention of 10 per cent or less — did well almost without exception. There were 43 operations in this group with only 1 case of liver failure and no "liver deaths" (lower part of Table 1 and Table 3).

On the other hand, liver failure, "liver death" or "hemorrhagic death" occurred in 7 cases after 39 operations (a rate of 18 per cent) with preoperative bromsulfalein retention of 11 to 20 per cent; after 54 operations on patients with more than 20 per cent retention, there were 17 of these complications — a rate of 32 per cent.

Other tests. There was but a single case of nonfatal liver failure after 24 operations on patients with negative or + cephalin-cholesterol flocculation. By contrast, "hemorrhagic death," "liver-death" or nonfatal liver failure occurred after 9 of 24 operations on patients with ++++ cephalin-cholesterol flocculation (a rate of 37 per cent). Marked disturbances in serum bilirubin and one-stage prothrombin time were also associated with a frequency of approximately 33 per cent liver failure, "liver death" or "hemorrhagic death" (Table 3). Normal values for these two tests, however, did not guarantee freedom from hepatic complications. Thirty-four operations were performed on patients with a serum bilirubin of 0.7 mg. per 100 ml. or less, of whom 3 suffered nonfatal postoperative liver failure and 1 died during surgery from massive hemorrhage. Similarly, postoperative liver failure or liver death occurred in 7 cases among 56 operations on patients with normal prothrombin times. Disturbances in serum alkaline phosphatase concentration, measured preoperatively in 101 cases, showed no correlation with operative or postoperative hepatic complications.

Thus, it has been possible to predict a good outcome for shunt surgery in patients with "mild" liver disease, and a poor outcome for patients with "severe" liver disease, leaving a large group of patients with "moderate" liver disease for whom a dependable prognosis is not as easily established. Eighty-eight operations were performed on this group, with 16 cases of liver failure (6 fatal) and 4 deaths from uncontrollable operative bleeding (lower part of Table 1). Although it has not been possible to predict the outcome for each patient in this group accurately, there were certain clear-cut prognostic clues.

The cephalin-cholesterol flocculation was particularly valuable. Thirty-three operations on patients with "moderate" liver disease and negative, + or ++ cephalin-cholesterol flocculation (in forty-eight hours), were followed by liver failure in 4 (12 per cent); 3 of these patients recovered, and 1 died. After 50 operations on patients with "moderate" liver disease and +++ or ++++ cephalin-cholesterol flocculation there were 12 cases of liver failure, of which 4 were fatal, and 4 operative deaths due to uncontrollable hemorrhage (liver failure, "liver death" or "hemorrhagic death" in 33 per cent).

To focus only on deaths, there was a 19 per cent mortality in patients with "moderate" liver disease and +++ or ++++ cephalin-cholesterol flocculation, and only a 3 per cent mortality in those with moderate liver disease and negative, + or ++ cephalin-cholesterol flocculation.

Similarly, the 88 patients with "moderate" liver disease could be divided into approximately equal numerical groups for mild and marked disturbances of each of the other liver-function tests. Serum albumin concentration below 4.0 gm. per 100 ml., bromsulfalein retention above 20 per cent and a one-stage prothrombin time below 75 per cent of normal were each associated with approximately a twofold increase in frequency of liver failure or liver death.

Physical Examination

The presence of spider angiomas, which were observed in about half the patients with moderate liver disease, was also associated with a twofold increase in postoperative liver failure (Table 4). The size of the liver proved a most impressive and surprising prognostic sign. The liver was palpable preoperatively in 68 of the 88 cases of "moderate liver disease," and all cases of liver failure or "hemorrhagic death" were among the 68 with palpable livers. The 20 operations on patients with moderate liver disease but nonpalpable livers were distinguished by their benign postoperative events.

Other items of physical examination showed less correlation with the outcome. We have found jaundice and ascites to be two factors that could usually be improved by preoperative preparation, and every effort was made not to operate on these patients until their jaundice and ascites had disappeared. In the small groups who had jaundice or ascites at the time of operation, there was no significant difference in the postoperative results as compared with those in whom neither of these findings was present.

Type of Anastomosis

A very important factor in determining the immediate operative outcome was the choice of type of anastomosis—portacaval or splenorenal (Table 5). There were 24 portacaval anastomoses in patients with moderate liver disease. Nine of these were followed by postoperative liver failure (fatal in 3), and 15 were uneventful or associated with complications unrelated to the liver. A splenorenal anastomosis was performed in 58 cases and was followed by liver failure in 7 (fatal in 2) and by "hemorrhagic death" in 2. Thus, in patients with "moderate" liver disease, 38 per cent of portacaval anastomoses were followed by liver failure or "liver death" whereas liver failure, "liver death" or "hemorrhagic death" occurred in only 16 per cent of splenorenal anastomoses. This marked difference in morbidity is probably attributable to the interruption of the portal vein and resultant derangement in hepatic circulation.

Combinations of Prognostic Factors

Factors that bore a clear-cut relation to postopera-

tive liver complications in patients with moderate liver disease, therefore, are as seen in the preceding paragraphs: abnormalities in cephalin-cholesterol flocculation, one-stage prothrombin activity, bromsulfalein retention and serum albumin; the presence of spider angiomas or an enlarged liver; and the type of anastomosis. Combinations of these factors were associated with a progressively increasing frequency of liver complications. For example, liver failure, "liver death" or "hemorrhagic death" occurred in 25 per cent for all cases of "moderate" liver disease. Thirty-nine per cent of patients with "moderate" liver disease, a palpable liver and + + + or + + + + cephalin-cholesterol flocculation suffered liver failure, "liver death" or "hemorrhagic death"; a portacaval anastomosis in patients with this combination was associated with a "mortality-morbidity" of 54 per cent. Conversely, the *absence* of more than one of these prognostic factors was associated with an increasingly favorable outcome. After 21 operations on patients with moderate liver disease, negative, + or + + cephalin-cholesterol flocculation and no spider angiomas, there were but 2 cases of liver failure (9 per cent).

It is clear that these prognostic factors are of great value in indicating trends. At the same time it is impossible always to predict how a given patient will fare. For example it was impressive that 3 of the 7 patients who had "moderate" liver disease and *all* the unfavorable prognostic factors summarized above survived surgery with an entirely uneventful course.

Other Factors

Age. A factor of rather less importance than those considered above, but of considerable interest, was the patient's age (Table 2). There were no deaths or liver failure after 28 operations on patients under the age of thirty—owing in part, at least, to the preponderance of extrahepatic portal-bed block in this age group. Although, in general, mortality and morbidity increased with increasing age, it was surprising that liver failure occurred in only 5 cases (being fatal in 3) among the 21 patients in the seventh or eighth decade.

Anesthesia. The choice of anesthetic agent showed surprisingly little effect on the outcome (Table 6). Postoperative liver failure occurred just as often after cyclopropane as when nitrous oxide, oxygen and ether were used. French and his associates,[1,2] working in this laboratory, have previously demonstrated that disturbances in liver function (as indicated by the bromsulfalein retention, serum bilirubin, urinary urobilinogen excretion, one-stage prothrombin time and serum alkaline phosphatase) are the same after ether or cyclopropane anesthesia. They concluded, "As far as the liver is concerned anesthesia is a very small part of the sum of stresses which add up to the total operative insult." Our clinical experience with these two anesthetic agents supports these conclusions and is contrary to the widespread but poorly documented belief that cyclopropane is the anesthetic of choice in the presence of liver disease.

During 1953 and 1954 most shunt surgery was performed under "hypotensive spinal anesthesia"—induced hypotension accomplished with high spinal anesthesia. The experience with this technic appears satisfactory. In previously published studies disturbances in postoperative liver-function tests were found to be the same or less than those after ether or cyclopropane anesthesia.[4] In the present study, the over-all operative mortality was almost identical for ether, cyclopropane and hypotensive spinal anesthesia, but nonfatal liver failure was considerably less frequent after hypotensive spinal anesthesia than after ether or cyclopropane (Table 6). There are a number of reasons why this may be an apparent rather than a real difference. Mortality and morbidity had fallen impressively in the years before the introduction of hypotensive spinal anesthesia, and, therefore, when the new technic is compared with cyclopropane or ether, it must be remembered that the hypotensive cases were all done with maximal benefit from improved medical and surgical procedures.

Another difficulty in comparing anesthetic agents is that there was some degree of selection of patients for the hypotensive technic. In the past two years, cyclopropane or ether anesthesia has been used in only 4 cases, with postoperative liver failure in 3. Of the 3 patients who did poorly, 2 did not receive hypotensive spinal anesthesia because they were considered to be "too poor risks."

"Hypotensive spinal" anesthesia was introduced by Griffiths and Gillies[5] in 1945 as a method of reducing operative blood loss. Gillies[6] himself has expressed the opinion that the technic is unsuitable for shunt surgery, and others have warned against the application of induced hypotension to patients with liver disease.[7] Thus, our successful use of hypotensive spinal anesthesia for shunt surgery has been somewhat contrary to expectations, and although we cannot say that it is better for the diseased liver, our experience strongly suggests that this form is no worse than other anesthetic technics. Since induced hypotension does provide enormously improved operative conditions for shunt surgery, including a significant decrease in number of blood transfusions necessary, its use is probably justified in cases in which there are no obvious contraindications.

Surgical shock. It was surprising to find that accidental hypotension, usually secondary to sudden, rapid blood loss, appeared to be reasonably well tolerated in many cases after the blood lost had been restored. Excluding the cases of hypotensive spinal anesthesia, the systolic blood pressure fell below 80 mm. of mercury during 24 of the operations. Five of these were on the patients, discussed above, who

died of uncontrollable massive capillary bleeding. One patient, classified as having "mild" liver disease, suffered cardiac arrest on two separate occasions during the induction of ether anesthesia. On each occasion cardiac massage was promptly and successfully instituted. Surgery was canceled the first time; the second time the proposed portacaval shunt was carried out and was followed by an uneventful postoperative course. Eighteen patients suffered brief to prolonged hypotension from blood loss (systolic pressure below 80 but usually above 60 mm. of mercury) during surgery or in the immediate postoperative period. Four of these 18 patients had "mild" liver disease and did well postoperatively. Postoperative liver failure or liver death occurred in 4 of 12 patients with "moderate" liver disease and in 1 of 2 patients with "severe" liver disease.

Summary and Conclusions

A study of the operative and immediate postoperative response of patients with portal hypertension and liver disease to venous-shunt surgery is presented. There were 129 patients, all but 6 of whom had bled massively from esophageal varices. Portal hypertension was on the basis of cirrhosis in 100 patients and secondary to extrahepatic portal-bed block (so-called Banti's syndrome) in 29. Preoperative studies included bromsulfalein retention, serum albumin, bilirubin and alkaline phosphatase concentrations, cephalin-cholesterol flocculation and one-stage prothrombin time. Preoperative preparation emphasized diet, rest and, when indicated, whole-blood transfusions and intravenous administration of human albumin. There were 83 splenorenal, 36 portacaval and 6 "makeshift" shunts, and 16 unsuccessful attempts to construct a shunt. Surgery was performed under ether, cyclopropane or, more recently, hypotensive spinal anesthesia. Postoperative treatment included use of oxygen by nasal catheter for twenty-four to forty-eight hours and adequate amounts of hypertonic dextrose intravenously, as well as support of fluids, electrolytes and red-cell volume.

Serious operative or postoperative complications directly related to the liver occurred in 27, or 19 per cent, of the operations. Frank liver failure developed in 22 patients, 8 of whom died. Five patients died during surgery of uncontrollable venous and capillary bleeding (all 5 in the first five years of the study —1945-1949—before the use of fresh blood became routine during shunt surgery). All but 2 of these complications were in patients with cirrhosis. The correlation of laboratory and physical findings with clinical results provided additional prognostic criteria. Preoperative bromsulfalein retention of 10 per cent or less gave a virtual (98 per cent) guarantee of freedom from postoperative liver complications. Conversely, a low serum albumin level preoperatively (below 3.0 gm. per 100 ml.) was associated with a prohibitively high (66 per cent) rate of hepatic complications. Preoperative disturbances in other liver-function tests were in general associated with increased frequency of postoperative liver failure but were of less specific prognostic value.

The choice of operation was a very important factor in determining the outcome. Postoperative liver failure in cirrhosis occurred twice as often after a portacaval as after a splenorenal anastomosis. In contrast, the choice of anesthetic agent had surprisingly little effect on the outcome. Liver failure followed cyclopropane as often as it did ether. The experience with hypotensive spinal anesthesia, used in most of the recent cases, has been as good as that with ether or cyclopropane, and, in view of the extraordinary technical difficulties of shunt surgery, induced hypotension is probably justified in cases in which there are no obvious contraindications.

References

1. French, A. B., et al. Metabolic effects of anesthesia in man. V. Comparison of effects of ether and cyclopropane anesthesia on abnormal liver. *Ann. Surg.* **135**:145-163, 1952.
2. Fairlie, C. W., Barss, T. P., French, A. B., Jones, C. M., and Beecher, H. K. Metabolic effects of anesthesia in man. IV. Comparison of effects of certain anesthetic agents on normal liver. *New Eng. J. Med.* **244**:615-622, 1951.
3. McDermott, W. V., Jr., Wareham, J., and Riddell, A. G. Treatment of "hepatic coma" with L-glutamic acid. *New Eng. J. Med.* **253**:1099-1102, 1955.
4. Greene, N. M., et al. Hypotensive spinal anesthesia: respiratory, metabolic, hepatic, renal, and cerebral effects. *Ann. Surg.* **140**: 641-651, 1954.
5. Griffiths, H. W. C., and Gillies, J. Thoraco-lumbar splanchnicectomy and sympathectomy: anaesthetic procedure. *Anaesthesia* **3**: 134-146, 1948.
6. Gillies, J. Discussion of hypotension in anaesthesia. *Brit. M. J.* **1**: 504, 1955.
7. Papper, E. M., and Ngai, S. H. Anesthesiology. *New Eng. J. Med.* **250**:991-996, 1036-1041 and 1071-1078, 1954.

STUDIES OF BACTERIAL THROAT FLORA DURING CHEMOPROPHYLAXIS OF RHEUMATIC FEVER*

JOSEPH M. MILLER, M.D.,† AND BENEDICT F. MASSELL, M.D.‡

BOSTON

THE well established relation between acute rheumatic fever and antecedent infection due to Group A hemolytic streptococci has resulted in the widely accepted use of continuous daily chemoprophylaxis for the prevention of rheumatic fever in susceptible persons. The two agents that have demonstrated the most practical application for such prophylaxis are sulfadiazine and penicillin by mouth, and the use of these drugs has now undergone extensive clinical trial. Many workers have reported a low rate of occurrence of hemolytic streptococcal infections in children receiving chemoprophylaxis,[1-12] but some questions persist regarding the potential dangers of such continuous prophylaxis.

The possibility that striking alterations in the bacterial flora in various regions of the body may follow the use of antibiotics is well documented,[13-23] and persons recovered from rheumatic fever and receiving sulfadiazine or penicillin continuously over long periods appear to be ideal subjects for such changes in bacterial populations. Thus, a regimen of long-continued therapy with penicillin might tend to eliminate susceptible gram-positive bacteria from the throat and nasopharynx and might theoretically invite the development of nonsensitive gram-negative organisms, which may flourish in an environment rendered more favorable by the absence of susceptible bacteria. In most cases such changes in local bacterial flora are not important, but under suitable conditions such resistant organisms may multiply, become predominant and even initiate clinical infection. Such infections that follow drug-induced alterations in bacterial flora have been termed "superinfections,"[22] and many accounts of this complication of chemotherapy have appeared.[13,14,22,23,24-29] In addition, reports concerning the development of mouth and tongue lesions attributable to penicillin[14,19,30-32] have caused further concern about the safety of long-term penicillin therapy in the prophylaxis of rheumatic fever.

The present report summarizes data concerning the throat flora of a group of subjects recovered from rheumatic fever and receiving either sulfadiazine or penicillin by mouth over prolonged periods and compares the flora with that of a group not receiving chemoprophylaxis. It is to be hoped that these results may refute objections about dangers of throat-flora alteration and may help establish the safety of rheumatic-fever chemoprophylaxis by means of documented bacteriologic evidence. This study does not include observations regarding changes in sensitivity to penicillin of the gram-positive organisms isolated from the throat flora during prolonged chemoprophylaxis.

TABLE 1. *Analysis of Patients in the Study.*

GROUP	TOTAL PATIENTS	PATIENTS WITH POTENTIAL RHEUMATIC HEART DISEASE	PATIENTS WITH VALVULAR HEART DISEASE OF RHEUMATIC ORIGIN	AVERAGE AGE	TOTAL DURATION OF TREATMENT	AVERAGE DURATION OF TREATMENT BEFORE 1ST CULTURE
				yr.	*mo.*	*mo.*
Penicillin	59	25	34	14.8	614	10.4
Sulfadiazine	60	29	31	13.8	455	7.6
Control*	94	37	57	28.0	—	—

*No treatment.

METHODS

Throat cultures were obtained from 213 patients with a definite past history of acute rheumatic fever who were seen at periodic intervals in the follow-up outpatient clinic of the House of the Good Samaritan. The study was conducted over a twelve-month period, —from February 1, 1952, until February 1, 1953,— which made possible a full four-season observation of variations in throat flora. The frequency of clinic visits and throat cultures in individual patients varied from one to thirty during the study period. The total number of patients has been divided into three groups (Table 1). The penicillin group included 59 patients who were receiving continuous buffered penicillin G prophylaxis by mouth in the amount of 100,000 units three times daily. The sulfadiazine group constituted 60 patients who received sulfadiazine, 0.5 gm., twice daily. The control group consisted of 94 patients who were not receiving daily chemoprophylaxis but instead were instructed to take penicillin at the first sign of

*From the House of the Good Samaritan, Children's Medical Center, and the departments of Pediatrics and Medicine, Harvard Medical School.

Aided by a grant from the Massachusetts Heart Association.

†Assistant in medicine, Harvard Medical School; research associate, House of the Good Samaritan.

‡Assistant clinical professor of pediatrics, Harvard Medical School; research director, House of the Good Samaritan.

an upper respiratory infection. The three groups of patients have been further divided into those having definite valvular heart disease of rheumatic origin and those having a definite or probable history of acute rheumatic fever, no evidence of residual valvular damage but merely potential rheumatic heart disease. On the average, the former were seen in the clinic more frequently than the latter during the one-year period. Also, patients taking sulfadiazine were seen, on the average, at more frequent intervals than the other groups because of the necessity of checking urine and blood count for possible sulfadiazine toxicity. The average age of the penicillin and sulfadiazine groups of patients was comparable whereas the control group not receiving prophylaxis tended to include a majority of older adults. The average duration of continuous prophylaxis before the start of the study was higher in the penicillin group (ten and four-tenths months) than in the sulfadiazine group (seven and six-tenths months). The minimum period of chemoprophylaxis for all patients before the first throat culture was one month. The relative frequency of throat cultures obtained from the three groups of patients is apparent from Table 2. It is obvious that the patients receiving sulfadiazine prophylaxis were seen more frequently during the one-year study period.

TABLE 2. *Relative Frequency of Throat Cultures during the Period of Study.*

GROUP	TOTAL PATIENTS	PATIENTS WITH 1 CULTURE	PATIENTS WITH 2 CULTURES	PATIENTS WITH 3 CULTURES	PATIENTS WITH MORE THAN 3 CULTURES
Penicillin	59	20	19	10	10
Sulfadiazine	60	6	10	7	37
Control	94	66	14	4	10

At each clinic visit, the oropharynx and tonsillar areas of each patient were swabbed by an experienced laboratory technician, and the swab was then inoculated and streaked onto an agar plate made by the addition of 5 per cent sheep blood to a fresh beef-heart infusion base. Although the use of sheep blood instead of horse blood is preferred in this laboratory because of the greater ease of recognition of beta-hemolytic streptococci, such sheep-blood plates do not support the growth of *Haemophilus influenzae*, and information concerning the presence of this organism is not included in these data. The coliform group of gram-negative bacteria grow well on this medium. In addition to the blood-agar plate, beef-heart infusion broth was inoculated with the throat swab during the first four months of the study to correlate the gram-stained smear of broth growth with the colony morphology on the blood-agar plates. After four months of correlation, it was thought that broth growth added little additional data to that obtained from the plates and this practice was discontinued.

After approximately eighteen hours of incubation at 37°C. the blood-agar plates were examined carefully by hand lens for colony characteristics, and the organisms present were noted arbitrarily as "predominant," "many," "few" or "isolated colonies." The *Diplococcus pneumoniae* offered the greatest difficulty in gross differentiation from *Streptococcus viridans*, and during the first four months of study final differentiation was made by correlation of suspected plate colonies with gram-stained broth smear. Beyond this period it was believed that the experience gained from such correlation made possible gross colony differentiation of *Str. viridans* and *D. pneumoniae* with a high percentage of accuracy. In all cases in which a gram-negative colony was suspected on the blood-agar plate, transfer was made to an eosin and methylene blue agar plate, and all confirmed colonies of gram-negative rods were finally classified by growth on the usual differential mediums.

No specific effort was made to evaluate the presence of monilia or other fungal growth by inocula-

TABLE 3. *Throat Cultures of Three Groups of Patients.*

ORGANISM	GROUP TREATED WITH PENICILLIN*		GROUP TREATED WITH SULFADIAZINE†		CONTROL GROUP‡	
	POSITIVE CULTURES	PATIENTS WITH POSITIVE CULTURES	POSITIVE CULTURES	PATIENTS WITH POSITIVE CULTURES	POSITIVE CULTURES	PATIENTS WITH POSITIVE CULTURES
Str. viridans	157 (97.5%)	59	245 (98.0%)	60	168 (98.2%)	94
Staphylococcus albus	141 (88.1%)	55	196 (78.4%)	56	145 (84.9%)	89
Staph. aureus (nonhemolytic)	30 (18.8%)	23	28 (11.2%)	24	21 (12.3%)	16
Staph. aureus (hemolytic)	16 (10.0%)	10	30 (12.0%)	22	5 (2.9%)	5
D. pneumoniae	7 (4.4%)	6	31 (12.4%)	24	21 (12.2%)	18
Beta-hemolytic streptococcus	0 (—)	0	0 (—)	0	2 (1.2%)	2
Gram-negative bacilli (coliform)	16 (10.0%)	6	1 (0.4%)	1	2 (1.2%)	2

*Total cultures, 160.
†Total cultures, 250.
‡Total cultures, 171.

tion of Sabouraud medium. Also, gram-negative cocci, although frequently present, were not systematically tabulated.

Results

The results of throat-culture data for all three groups of rheumatic subjects are listed in Table 3 and depicted graphically in Figure 1. The total number of throat cultures taken in the penicillin and control groups is quite comparable whereas more observations were made in the sulfadiazine group, reflecting the greater frequency of clinic visits by this patient group.

The two most prevalent organisms detected in the throats of all three groups of patients were *Str. viridans* and *Staph. albus;* the percentage of cultures containing these two organisms was also roughly the same in all groups. The occurrence of nonhemolytic *Staph. aureus* was essentially equal in the sulfadiazine and control groups but somewhat greater in subjects receiving daily penicillin. However, the penicillin and sulfadiazine groups showed a similar low occurrence of hemolytic *Staph. aureus* (10.0 and 12.0 per cent) whereas the control group demonstrated only a rare culture positive for this bacterium (2.9 per cent). Data for *D. pneumoniae* strongly suggest an effective suppression of this organism by daily small doses of penicillin (4.4 per cent), whereas the sulfadiazine and control groups demonstrated a comparatively higher rate of occurrence (12.4 and 12.2 per cent). Over this one-year period of sampling without regard for presence or absence of clinical infection, not a single case of a Group A beta-hemolytic streptococcus was isolated from both groups receiving chemoprophylaxis. Two such positive cultures were noted in the control group and were promptly eradicated by oral treatment with penicillin.

Since much emphasis has heretofore been placed on possible gram-negative alteration of throat flora after continuous antibiotic regimens, the data for these coliform organisms shown in Table 3 have been analyzed separately in Table 4. It is apparent that there was a 10 per cent frequency of cultures showing gram-negative bacteria in the penicillin group as compared to a single such culture in the sulfadiazine group (0.4 per cent) and only 2 such cultures in the control group (1.2 per cent). This 10 per cent prevalence of gram-negative organisms applied to the total cultures as well as to the number of patients receiving penicillin. These differences are statistically significant at the 5 per cent level.* Of these 16 cultures of the penicillin group, 6 showed *A. aerogenes,* 9 were positive for *Esch. coli* and a single culture grew *Ps. aeruginosa.* In only 3 cases (*A. aerogenes*) was the gram-negative organism found to be predominant. These findings contrasted with a single case in which *Esch. coli* was present as a "few" colonies in the entire sulfadiazine group and a single case each of *Ps. aeruginosa* and *K. pneumoniae* in the control group. There was no apparent episode of clinical superinfection of the respiratory tract by

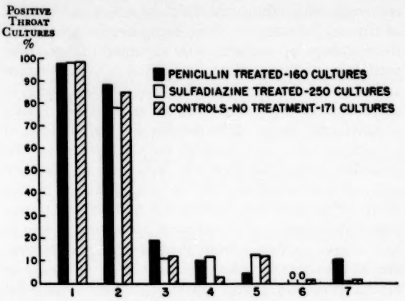

Figure 1. *Throat Flora during Chemoprophylaxis of Rheumatic Fever.*
1=Str. viridans; *2*= Staph. albus; *3*=*nonhemolytic* Staph. aureus; *4*=*hemolytic* Staph. aureus; *5*=D. pneumoniae; *6*=*beta-hemolytic streptococcus; 7*=*gram-negative bacilli (coliform).*

Table 4. *Analysis of Gram-Negative Coliform Bacteria.*

Group	Total Patients Harboring Coliform Bacteria	Total Cultures Containing Coliform Bacteria	Cultures Containing *Aerobacter aerogenes*					Cultures Containing *Escherichia coli*					Cultures Containing *Proteus vulgaris*	Cultures Containing *Pseudomonas aeruginosa*	Cultures Containing *Klebsiella pneumoniae*
			Total	As Predominant Organism	Many Colonies	Few Colonies	Isolated Growth	Total	As Predominant Organism	Many Colonies	Few Colonies	Isolated Growth			
Penicillin	6	16	6	3	1	1	1	9	0	1	8	0	1*	—	—
Sulfadiazine	1	1	—	—	—	—	—	1	0	0	1	0	—	—	—
Control	2	2	—	—	—	—	—	—	—	—	—	—	—	1*	1†

*Few colonies.
†Isolated growth.

ture grew *Ps. aeruginosa.* In only 3 cases (*A. aerogenes*) was the gram-negative organism found to be predominant. These findings contrasted with a single case in which *Esch. coli* was present as a "few" colonies in the entire sulfadiazine group and a single case each of *Ps. aeruginosa* and *K. pneumoniae* in the control group. There was no apparent episode of clinical superinfection of the respiratory tract by

*Statistical studies performed by Dr. William E. Reynolds, formerly assistant professor of preventive medicine, Harvard Medical School.

gram-negative organisms in the entire 213 patients observed.

Discussion

In spite of the statistically significant increase in the number of coliform bacteria among the patients receiving penicillin prophylaxis, there was no evidence of clinical infection by these organisms in any of the three groups of subjects with rheumatic fever. The predominant throat flora, consisting of *Str. viridans* and *Staph. albus*, remained essentially the same in subjects receiving prophylaxis as in those not taking prophylactic drugs. The somewhat higher rate of occurrence of nonhemolytic *Staph. aureus* in the penicillin-treated subjects did not seem to correlate with clinical superinfection by this organism in this study. The same lack of clinical manifestations was found in relation to the increased prevalence of hemolytic *Staph. aureus* in both drug-treated groups over that of the controls. The lower rate of *D. pneumoniae* in the penicillin group confirms reports about the extreme sensitivity of this bacterium to penicillin. Lack of a single case of a culture positive for Group A hemolytic streptococci in treated patients confirms the efficacy and rationale of chemoprophylaxis in patients recently recovered from acute rheumatic fever. The finding of only 2 cases of such streptococcal infection in the nontreated control group may be attributed to the occasional sampling of throat cultures at routine visits, additional infections having been eradicated by the patients themselves in following instructions of their family physicians to take therapeutic amounts of penicillin by mouth at the time of acute upper respiratory infections. The detection of 2 such positive cultures in asymptomatic persons serves to demonstrate the possible subclinical nature of infection with hemolytic streptococci and points up the importance of chemoprophylaxis.

The observed frequency (10 per cent) of gram-negative bacteria in the throat flora of persons taking continuous penicillin, as compared to the very rare finding of such organisms in the other two groups, may be interpreted as a definite biologic alteration of throat flora by penicillin. This low prevalence of throat-flora change is at variance with the findings of others and hence warrants some interpretation. Lipman, Coss and Boots[17,18] gave 500,000 to 1,000,000 units of penicillin daily by mouth to 10 subjects with rheumatoid arthritis and noted a sudden early change in throat flora from gram-positive to gram-negative coliform bacteria in 9 of the 10 subjects. These coliform organisms often became predominant, but cessation of penicillin therapy resulted in the reappearance of gram-positive cocci in all throat flora. Likewise, Haffner et al.[16] demonstrated a change to gram-negative throat flora in 30 of 68 unselected children given penicillin for various respiratory illnesses. It is noteworthy that 9 of these patients demonstrating throat-flora conversion had received penicillin by the aerosol route. Also, Smith and Bloomfield[20] gave 360,000 to 1,200,000 units of penicillin by the intramuscular route to 6 normal subjects and reported that all subjects showed the appearance of coliform bacilli in the throat during treatment, thus demonstrating the profound change in the "balance of power" caused by the antibiotic. A similar effect of intramuscular penicillin is reported by Long[21] and Weinstein.[22,29]

An inspection of the details of such reported cases and explanations of results offered by the authors themselves serves to point up obvious factors that may account for the very few cases of gram-negative conversion in the present study. The higher oral dosage used by Lipman et al.[17-19] would favor higher blood levels of penicillin, with a more potent bactericidal effect on sensitive gram-positive cocci of the throat. Prophylactic dosage of penicillin used for rheumatic subjects appears to be effective for preventing infection with the highly sensitive hemolytic streptococcus and at the same time allows for submaximal suppression of other gram-positive cocci. Haffner, Neter and Rubin[16] do not indicate the dosage of penicillin used but stress the observation that children with gram-negative conversion were more severely ill before therapy and that hospitalized patients may be exposed to ward contamination as a source of their gram-negative throat flora. Neither of these conditions prevails in healthy ambulatory rheumatic subjects. The intramuscular route of administration and the higher dosage of penicillin employed by Smith and Bloomfield[20] would also result in higher blood levels and, hence, might explain why gram-negative conversions were more frequent than in the present study.

Weinstein[22] stresses age and chronic debilitating disease as two important predisposing factors in both throat-flora alteration and the development of superinfection. His studies have shown that children under two years of age, as well as senile patients, are more apt to react adversely to antibiotic alterations of throat flora.[29] Others, too, have described superinfections as occurring primarily in elderly and chronically ill patients.[14,25,26] Ambulatory subjects recovered from rheumatic fever and receiving prophylaxis usually do not fulfill either of these predisposing criteria for possible gram-negative overgrowth.

In addition to the potential dangers of gram-negative bacterial alteration after the continuous use of antibiotics, references have appeared on fungal complications.[29-35] These complications have ranged from the more serious cases of superinfection[29,31] to the observations of benign secondary mouth and tongue lesions that are easily reversible by cessation of the offending drug.[14,19,30,32] As with coliform organisms, some have speculated that suppression of sensitive bacterial flora coexisting with candida and competing for nutrition in the same substrate may be the cause of monilial overgrowth in the mouth and generalized

host infection.[31] Foley and Winter[35] have even demonstrated an increased mortality after penicillin therapy of chick embryos infected with *Candida albicans*. Although fungal-culture data were lacking in the present survey of subjects receiving continuous penicillin, tongue or other mucous-membrane manifestations were not observed, nor were such symptoms described by the patients.

The explanation of the absence of such complications in these rheumatic subjects may be found in the selection of drug employed and the route of administration. Most cases of clinical superinfection with fungal organisms have followed the use of the broad-spectrum antibiotics rather than penicillin, and Weinstein[29] also describes penicillin as having the least predisposing effect on superinfection. Finally, practically all descriptions of black, hairy tongue, stomatitis and glossitis can be traced to the use of penicillin in the form of troches, lozenges, pastilles or aerosol sprays.[14,30,33] It appears, therefore, that a small prophylactic dose of penicillin by mouth, as employed in this study, involves few of the conditions conducive to fungal complications.

Summary and Conclusions

Long-term chemoprophylaxis of ambulatory patients with rheumatic fever by means of sulfadiazine or penicillin by mouth effects no major change in bacterial throat flora that may predispose such persons to serious superinfection.

The predominant bacterial flora of the throat in treated subjects of this study remained essentially the same as that in subjects not receiving prophylaxis.

Nonhemolytic *Staphylococcus aureus* was slightly more frequent in the group receiving penicillin than in groups receiving sulfadiazine or no prophylaxis.

The occurrence of hemolytic *Staph. aureus* was approximately equal in both groups receiving prophylaxis, and this organism was present to a higher degree in both these groups than in the control group not receiving prophylaxis.

The prophylactic dose of penicillin employed in this study appeared to suppress *Diplococcus pneumoniae* to a level of prevalence below that of the control group and the sulfadiazine group.

After sampling of throat cultures in these subjects no case of a positive culture for Group A beta-hemolytic streptococcus was detected in either group receiving chemoprophylaxis. Two such cultures were observed in the control group.

Prophylactic administration of penicillin appeared to result in a low but definitely higher prevalence of gram-negative coliform bacilli in the throat flora as compared to the other two groups of patients. Rarely did these coliform bacilli become the predominant flora.

The reasons for this low rate of gram-negative conversion are discussed in relation to reports in the literature regarding dangers of throat-flora alterations as an antecedent to superinfection.

The absence of clinical evidence of fungal complications of the mouth in rheumatic-fever patients receiving prophylaxis is explained in the light of factors that obviously predispose to such oral lesions.

The data obtained in this study emphasize the safety of chemoprophylaxis of rheumatic fever so far as secondary bacterial complications are concerned.

We are indebted to Miss Doris M. McCarthy for the technical assistance rendered in this study.

References

1. Coburn, A. F., and Moore, L. V. Prophylactic use of sulfanilamide in streptococcal respiratory infections, with especial reference to rheumatic fever. *J. Clin. Investigation* **18**:147-155, 1939.
2. Thomas, C. B., France, R., and Reichsman, F. Prophylactic use of sulfonamide in patients susceptible to rheumatic fever. *J.A.M.A.* **116**:551-560, 1941.
3. Kuttner, A. G., and Reyersbach, G. Prevention of streptococcal upper respiratory infections and rheumatic recurrences in rheumatic children by prophylactic use of sulfanilamide. *J. Clin. Investigation* **22**:77-85, 1943.
4. Baldwin, J. S. Sulfadiazine prophylaxis in children and adolescents with inactive rheumatic fever. *J. Pediat.* **30**:284-288, 1947.
5. Breese, B. B., et al. Prevention of rheumatic fever. *Mod. Concepts Cardiovas. Dis.* **22**:158-161, 1953.
6. Maliner, M. M. Oral penicillin in prophylaxis of rheumatic fever. *J. Pediat.* **37**:858-861, 1950.
7. Massell, B. F., Dow, J. W., and Jones, T. D. Orally administered penicillin in patients with rheumatic fever. *J.A.M.A.* **138**:1030-1036, 1948.
8. Massell, B. F. Present status of penicillin prophylaxis of rheumatic fever. *Mod. Concepts Cardiovas. Dis.* **20**:108, 1951.
9. Hofer, J. W. Oral penicillin for children with rheumatic fever. *J. Pediat.* **35**:135-144, 1949.
10. Brick, M., McKinley, H., Gourley, M., Roy, T. E., and Keith, J. D. Oral penicillin prophylaxis in rheumatic fever patients. *Canad. M. A. J.* **63**:255-258, 1950.
11. Gale, A. H., Gillespie, W. A., and Perry, C. B. Oral penicillin in prophylaxis of streptococcal infection in rheumatic children. *Lancet* **2**:61-63, 1952.
12. Miller, J. M., O'Connell, P. A., Kaplan, M. H., and Massell, B. F. Prevention of streptococcal infection and rheumatic fever with oral penicillin: progress report. In *Antibiotics Annual 1954-1955: Proceedings of second annual symposium on antibiotics.* Edited by H. Welch and F. Martí-Ibáñez. 1154 pp. New York: Medical Encyclopedia, Inc., 1955. Pp. 105-110.
13. Keefer, C. S. Alterations in normal bacterial flora of man and secondary infections during antibiotic therapy. *Am. J. Med.* **11**: 665, 1951.
14. Smith, D. T. Disturbance of normal bacterial ecology by administration of antibiotics with development of new clinical syndromes. *Ann. Int. Med.* **37**:1135-1143, 1952.
15. McCurdy, R. S., and Neter, E. Effects of penicillin and broad-spectrum antibiotics on emergence of gram-negative bacillary flora in upper respiratory tracts of infants. *Pediatrics* **9**:572-576, 1952.
16. Haffner, F. D., Neter, E., and Rubin, M. I. Penicillin and its effect in producing predominant gram-negative bacillary flora in upper respiratory tract of infants. *Pediatrics* **6**:262-268, 1950.
17. Lipman, M. O., Coss, J. A., Jr., and Boots, R. H. Changes in bacterial flora of throat and intestinal tract during prolonged oral administration of penicillin. *J. Bact.* **51**:594, 1946.
18. *Idem.* Changes in bacterial flora of throat and intestinal tract during prolonged oral administration of penicillin. *Am. J. Med.* **4**:702-709, 1948.
19. Coss, J. A., Jr., Bauman, E., Boots, R. H., and Lipman, M. O. Prolonged administration of penicillin in arthritis. *Am. J. Med.* **4**:710-715, 1948.
20. Smith, J. W., and Bloomfield, A. L. Effect of penicillin on aerobic bacterial flora of normal throat. *Stanford M. Bull.* **6**: 469-480, 1948.
21. Long, D. A. Effect of penicillin on bacterial flora of mouth. *Brit. M. J.* **2**:819-821, 1947.
22. Weinstein, L. Spontaneous occurrence of new bacterial infections during course of treatment with streptomycin or penicillin. *Am. J. M. Sc.* **214**:56-63, 1947.
23. Meads, M., Rowe, W. P., and Haslam, N. M. Alterations in bacterial flora of throat during oral therapy with aureomycin. *Arch. Int. Med.* **87**:533-540, 1951.
24. Stanley, M. M. Bacillus pyocyaneus infections: review, report of cases and discussion of newer therapy including streptomycin. *Am. J. Med.* **2**:253-277 and 347-367, 1947.
25. Sommer, L. S., and Favour, C. B. Biologic complications of penicillin therapy. *Am. J. Med.* **7**:511-517, 1949.
26. Yow, E. M. Development of proteus and pseudomonas infections during antibiotic therapy. *J.A.M.A.* **149**:1184-1188, 1952.
27. Garrard, S. D., Richmond, J. B., and Hirsch, M. M. Pseudomonas aeruginosa infections as complication of therapy in pancreatic fibrosis (mucoviscidosis). *Pediatrics* **8**:482-488, 1951.
28. Appelbaum, E., and Leff, W. A. Occurrence of superinfections during antibiotic therapy. *J.A.M.A.* **138**:119-121, 1949.
29. Weinstein, L., Goldfield, M., and Chang, T. Infections occurring during chemotherapy: study of their frequency, type, and predisposing factors. *New Eng. J. Med.* **251**:247-255, 1954.

30. Cross, W. G. Oral reactions to penicillin. *Brit. M. J.* **1**:171-173, 1949.
31. Woods, J. W., Manning, I. H., and Patterson, C. N. Monilial infections complicating therapeutic use of antibiotics. *J.A.M.A.* **145**:207-211, 1951.
32. Wolfson, S. A. Black hairy tongue associated with penicillin therapy. *J.A.M.A.* **140**:1206-1208, 1949.
33. Editorial. Fungus infections complicating antibiotic therapy. *J.A.M.A.* **149**:762, 1952.
34. Kligman, A. M. Are fungus infections increasing as result of antibiotic therapy? *J.A.M.A.* **149**:979-983, 1952.
35. Foley, G. E., and Winter, W. D., Jr. Increased mortality following penicillin therapy of chick embryos infected with *Candida albicans* var. *Stellatoidea*. *J. Infect. Dis.* **85**:268-274, 1949.

SURGERY OF THE BILIARY TRACT

I. Mortality and Complications of Cholecystectomy and Choledochostomy for Chronic Cholecystitis

MARSHALL K. BARTLETT, M.D.,* AND WILLIAM C. QUINBY, JR., M.D.†

BOSTON

SURGERY for chronic cholecystitis and cholelithiasis has become safer for the patient in recent years chiefly because of a better understanding of blood, fluid and electrolyte replacement, the use of antibiotics and improvements in anesthesia. In spite of these advances, definite risks remain, and continuing efforts must be made to reduce them to a minimum. The purpose of this study was to evaluate the experience with cholecystectomy and choledochostomy for chronic cholecystitis at the Massachusetts General Hospital for the eleven-year period 1943-1953, with particular reference to mortality and complications. It was hoped that a critical study of these factors would point the way to a further reduction of the risks involved.

MATERIAL

During this eleven-year period, 2243 operations were done for chronic cholecystitis — cholecystectomy alone on 1280 patients, and cholecystectomy with choledochostomy on an additional 963. The clinical, operative and pathological records were reviewed in each case. A few patients whose biliary-tract surgery was clearly incidental to other abdominal operative procedures were excluded. Patients who had previously had acute pancreatitis and on whom elective biliary-tract surgery was later done were included. Also excluded were 45 patients with carcinoma of the gall bladder who were operated upon in the same eleven-year period. In relation to the number of patients operated upon for chronic cholecystitis, this is an incidence of 1:50, or 2.0 per cent.

RESULTS

Over 90 per cent of all patients with chronic cholecystitis had gallstones in some part of the biliary system. The common bile duct was explored in 43 per cent of all cases, and stones were removed from 38 per cent of the ducts explored. Thus, 16 per cent of all patients had common-duct stones removed at operation.

*Clinical associate in surgery, Harvard Medical School; visiting surgeon, Massachusetts General Hospital.
†Instructor in surgery, Harvard Medical School; assistant in surgery, Massachusetts General Hospital.

Cholecystectomy was done in 1280 cases, with 8 deaths, a mortality of 0.6 per cent. These 8 patients ranged in age from fifty to eighty-two years. One died of sepsis within the abdomen. The other 7 died of causes not directly related to the specific operation performed, 5 dying of sudden cardiac catastrophes and 2 of massive pulmonary emboli. The cause of death was established by autopsy in 2 of the 8 cases and was reasonably certain on clinical grounds in the remaining 6.

In addition to these 8 deaths there were 113 nonfatal complications, which are analyzed in Table 1. Complications directly related to the operative procedure accounted for over half the total with wound sepsis heading the list. The incidence of complications was 8.9 per cent.

The median postoperative stay in the hospital for 1272 patients who survived operation was twelve days.

Cholecystectomy with choledochostomy was the operative procedure in 963 cases. There were 17 deaths — a mortality of 1.8 per cent. Autopsies were performed in 15 cases. Nearly half these deaths were from causes directly related to the operative procedure whereas the other half were only indirectly related to the operation (Table 2). Eleven patients were over sixty, 4 were between fifty and sixty, and only 2 were under fifty years of age.

A recognizable technical error was a factor in 2 of the deaths. In 1 the common duct was explored through the stump of the cystic duct, which later became necrotic, and a fatal bile peritonitis resulted. In another case a false passage was made into the head of the pancreas through the common-duct wall during exploration. A fatal pancreatitis ensued.

Six of the 17 patients who died after cholecystectomy with choledochostomy had had stones removed from the common duct. Thus, there was no significant difference in the operative mortality in cases with and those without stones found on choledochostomy.

Nonfatal complications occurred in 94 cases, or 9.8 per cent. As in the group of patients having cholecystectomy alone, wound complications, particularly sepsis, played an important part (Table 1).

The median postoperative hospital stay for the 946 patients who survived operation was fourteen days.

Discussion

Nonfatal complications occurring after cholecystectomy were almost equally divided between those directly related to the local operative procedure and those only indirectly related to the operation, and represent the hazards of any major abdominal surgery. After cholecystectomy with choledochostomy the former type of complication outnumbered the latter by two to one, and the total occurrence was somewhat greater, as would be expected from the additional manipulation involved. Of particular interest are the cases of residual common-duct stones. These will be included in detail in a later report.

The mortality rates of 0.6 per cent for cholecystectomy and 1.8 per cent for cholecystectomy with choledochostomy for chronic cholecystitis correspond closely with those in many recent reports in the literature,[1-10] and show a gratifying decrease since the last report from this hospital.[11]

Table 1. *Complications.*

Complication	Cholecystectomy		Cholecystectomy and Choledochostomy	
Directly related to operative procedure:				
Wound		39		36
Sepsis	32		28	
Hemorrhage	4		1	
Dehiscence	3		7	
Intra-abdominal		14		16
Hemorrhage	0		2	
Rt.-upper-quadrant abscess	6		2	
Peritonitis	0		1	
Pancreatitis	0		4	
Unexplained fever	8		7	
Biliary system		9		11
Common-duct injury	1		0	
Abnormal bile drainage	3		2	
Residual common-duct stone	4		6	
Duodenal fistula	0		1	
Cholangitis	1		0	
Miscellaneous	0		2	
Totals	62		63	
Indirectly related to operative procedure:				
Pulmonary		22		12
Atelectasis	9		9	
Infarct	10		2	
Pneumonia	2		0	
Pleurisy	1		1	
Other		29		19
Cardiac	1		1	
Gastrointestinal	4		1	
Genitourinary	8		4	
Neuromuscular	4		2	
Phlebitis	10		5	
Miscellaneous	2		6	
Totals	51		31	
Grand totals		113 (8.9%*)		94 (9.8%*)

*Percentage of all patients surviving operation.

Death attributable directly to the operative procedure occurred in only 1 of the patients who died after cholecystectomy. Since all 8 were over fifty years of age, the risk of cardiac or embolic catastrophe might have been less if those with symptoms of long duration had received surgical attention at an earlier age. In others, however, symptoms were of only a few weeks' or months' duration, and surgery was undertaken promptly. No general conclusion can be drawn except that, as in all major surgery, the cardiac, renal and pulmonary status of the patient must be carefully evaluated before operation.

Deaths after cholecystectomy with choledochostomy present even more of a challenge. Here, the mortality rate is three times that of cholecystectomy alone. Also, only 38 per cent of the ducts explored yielded stones. In some other cases it was undoubtedly essential to establish the patency and caliber of the papilla of Vater, but it may be fair to say that exploration of the common duct was unnecessary in half the cases. At the same time, as shown in Table 2, 9 of the 17 postoperative deaths were caused by factors directly related to the operation since they were due to postoperative pancreatitis, bile peritonitis and sepsis.

Table 2. *Causes of Death in 963 Cases of Cholecystectomy and Choledochostomy.*

Cause	Total Cases	Cases with Common-Duct Stones Present	Cases with No Common-Duct Stones Present
Postoperative pancreatitis	4	1	3
Bile peritonitis	2	1	1
Peritonitis	2	1	1
Retroperitoneal sepsis	1	1	0
Homologous serum jaundice	1	0	1
Bronchopneumonia	2	0	2
Cardiac complications	3	1	2
Liver failure	1	0	1
Renal failure	1	1	0
Totals	17	6	11

In this study the mortality of cholecystectomy with choledochostomy was essentially the same when the common duct failed to yield stones as when stones were found and removed. This differs from various previous reports,[5,7,8] including one from this hospital,[11] which have shown no significant increase in mortality when a negative choledochostomy was done at the time of cholecystectomy. This may be of little significance since the number of cases is small, but it is of some interest to analyze the causes of death on this basis (Table 2). Deaths directly attributable to the operative procedure predominated in patients with common-duct stones, whereas deaths from the general hazards of major abdominal surgery were more common in patients with negative common-duct explorations.

Four lines of attack suggest themselves as possible means of reducing this death rate. Operation earlier in the course of the disease, before the indications for common-duct exploration are present and earlier in the life of the patient would reduce the

risk. About half the 17 patients who died had symptoms of biliary-tract disease going back for several to many years, and only 2 of them were under fifty years of age. This approach has been stressed many times in the past,[10,12] and any progress along these lines must depend on greater efforts on the part of the practicing physicians and surgeons who see these patients.

Obesity is a well recognized factor in increasing operative morbidity and mortality, and for such patients a carefully supervised program of weight reduction before an elective operation on the biliary tree should decrease the risks involved.

Constant reappraisal of the indications for common-duct exploration is indicated. Secondary exploration of the duct for residual stones, when necessary, has carried a very low mortality in our experience, although it does involve further hardship and economic loss to the person involved. Also, of the 1280 patients who had a cholecystectomy without duct exploration, only 4 have returned to this hospital for removal of residual common-duct stones not recognized at the time of cholecystectomy. This is not an absolute figure since not all patients have been followed and others may have gone elsewhere for further surgery, but it does suggest that the number of common-duct stones overlooked because the duct was not explored is very small. These factors, with the added evidence that over half the duct explorations were unproductive of stones, leaves little cause for satisfaction with our present indications for this procedure. Considerable effort has been spent in developing operative cholangiography in the hope that it would provide an accurate substitute for mechanical exploration of the biliary tree.[13-18] Thus far the evidence does not clearly indicate that a sufficient degree of accuracy has been attained, but further technical advances may make it so.

Further improvement in the technic of common-duct exploration must be sought, since a substantial number of deaths are directly related to the operative procedure. Postoperative pancreatitis, bile leakage and sepsis are the chief technical pitfalls at present. The need for extreme gentleness and meticulous handling of tissues in this procedure must be constantly stressed. In competent hands a gentle transduodenal exploration of the papilla of Vater is far safer than a traumatic dilatation through a choledochotomy.

Summary

The experience with cholecystectomy and choledochostomy for chronic cholecystitis at the Massachusetts General Hospital for the eleven-year period 1943-1953 is presented.

Cholecystectomy was done in 1280 cases, with a mortality of 0.6 per cent. Nonfatal complications occurred in 8.9 per cent of those patients.

Cholecystectomy and choledochostomy were done in 963 cases. The mortality was 1.8 per cent, and nonfatal complications occurred in an additional 9.8 per cent of cases.

Factors involved in the postoperative deaths are discussed, and suggestions are made for reducing the risk of cholecystectomy and choledochostomy.

Operation at an earlier age and earlier in the course of the disease is urged for patients with chronic cholecystitis and cholelithiasis, as a means of reducing the morbidity and mortality of these conditions.

The rate of occurrence of carcinoma of the gall bladder was 2.0 per cent. Since this occurs almost exclusively in diseased gall bladders containing stones, it is an additional factor that must be considered when one advises surgery for patients with chronic cholecystitis.

References

1. Cole, W. H. Recent trends in gallbladder surgery. *J.A.M.A.* **150**: 631-637, 1952.
2. Glenn, F., and Hays, D. M. Causes of death following biliary tract surgery for nonmalignant disease. *Surg., Gynec. & Obst.* **94**: 283-296, 1952.
3. Glenn, F. Common duct exploration for stones. *Surg., Gynec. & Obst.* **95**:431-438, 1952.
4. McKittrick, L. S., and Wilson, N. J. Indications for and results following exploration of common bile duct for stones. *California Med.* **71**:132-137, 1949.
5. Priestley, J. T., Walters, W., Gray, H. K., and Waugh, J. M. Annual report on surgery of biliary system and pancreas for 1950. *Proc. Staff Meet., Mayo Clin.* **26**:505-513, 1951.
6. Thompson, R. H. Gall-bladder surgery in community hospital. *New Eng. J. Med.* **244**:347-351, 1951.
7. Waugh, J. M., Walters, W., Gray, H. K., and Priestley, J. T. Annual report on surgery of biliary system and pancreas for 1951. *Proc. Staff Meet., Mayo Clin.* **27**:578-584, 1952.
8. *Idem.* Annual report on surgery of biliary system and pancreas for 1951. *Proc. Staff Meet., Mayo Clin.* **28**:765-768, 1953.
9. Waugh, J. M., Johnston, E. V., and Cain, J. C. Surgical aspects of choledocholithiasis. *J.A.M.A.* **154**:734-738, 1954.
10. Zollinger, R. M., Boles, E. T., and Crawford, G. B. Diagnosis and management of biliary-tract disease. *New Eng. J. Med.* **252**: 203-208, 1955.
11. Wallace, R. H., and Allen, A. W. Acute cholecystitis. *Arch. Surg.* **43**:762-772, 1941.
12. Glenn, F., and Hays, D. M. Age factor in mortality rate of patients undergoing surgery of biliary tract. *Surg., Gynec. & Obst.* **100**:11-18, 1955.
13. Carter, R. F., and Gillette, L. Immediate cholangiography: indications, technic and illustrative cases. *J.A.M.A.* **143**:951-954, 1950.
14. Hight, D., and Lingley, J. R. Value of cholangiograms during biliary-tract surgery. *New Eng. J. Med.* **246**:761-765, 1952.
15. Johnston, E. V., Waugh, J. M., and Good, C. A. Residual stones in common bile duct: question of operative cholangiograms. *Ann. Surg.* **139**:293-301, 1954.
16. Mixter, C. G., Hermanson, L., and Segel, A. L. Operative cholangiography: evaluation of 406 cases. *Ann. Surg.* **134**:346-350, 1951.
17. Partington, P. F., and Sachs, M. D. Routine use of operative cholangiography. *Surg., Gynec. & Obst.* **87**:299-307, 1948.
18. Schlicke, C. P. Secondary operations on biliary tract. *Am. J. Surg.* **85**:754-759, 1953.

USE OF PROGESTERONE IN THE TREATMENT OF POST-PARTUM PSYCHOSIS*

WILLIS H. BOWER, M.D.,† AND MARK D. ALTSCHULE, M.D.‡

WAVERLEY AND BOSTON, MASSACHUSETTS

STUDIES previously made at this hospital suggest that the adrenal cortex is hyperactive in early but not in chronic schizophrenic, manic-depressive and involutional psychoses.[1] Nevertheless, although adrenocortical dysfunction in general often causes mental changes (the psychologic disorders accompanying Addison's and Cushing's diseases are well known), in the "functional" psychoses the adrenal factor is peripheral and is not of primary etiologic significance.[1] On the other hand, the administration of large amounts of testosterone, a steroid hormone that depresses pituitary-adrenocortical function, often results in improvement in patients with "functional" psychoses of recent onset — as was shown in a study made here about ten years ago.[2]

Six years ago observations were begun on the possible effectiveness of progesterone in women with these psychoses. At first no specific connection was observed between progesterone and remission of post-partum psychosis, but it soon became evident that striking benefit could be achieved through the use of the hormone in this particular condition. The present report is based on an analysis of the records of patients with this illness.

MATERIAL AND METHODS

A total of 39 women with post-partum psychoses were studied. Thirty-seven were patients at the McLean Hospital; 2 were patients at other hospitals but were treated by their physicians in accordance with our recommendations. For the most part only patients who had become psychotic during the first few weeks of the post-partum period were included. However, there were 2 exceptions — women who showed personality difficulty during the puerperium but manifested no overt psychosis until six and eight months after delivery; these 2 were among those treated with progesterone. Excluded from the study were patients who had become psychotic during pregnancy. Symptoms in the patients studied were varied. Most patients had feelings of marked depression; suicidal tendencies were common. Some were primarily overactive; a few were catatonic in behavior. Delusions of varying degrees of bizarreness were common. It is worthy of note that most of these women had apparently had good, or at least adequate, personality organization before delivery.

Treatment of the 39 patients was varied; 16 received progesterone alone or in combination with other therapy. Because ideas differed among the staff psychiatrists in charge of individual patients at various times, no consistent program of treatment was followed in these cases. Accordingly, Tables 1 and 2 show a variety of combinations of psychotherapy, electric shock, administration of insulin on an ambulatory basis and progesterone. Psychotherapy was attempted in most cases, although this is shown in Tables 1 and 2 only if unaccompanied by somatic treatment.

TABLE 1. *Results in 23 Patients Who Did Not Receive Progesterone.*

No. of Cases	Initial Treatment	Result	Later Treatment	Result
4	Psychotherapy	Remission maintained		
2	Electroshock	Remission maintained		
1	Electroshock	Remission, then relapse (suicide)		
7	Insulin	Remission maintained		
1	Insulin	Patient somewhat improved; discharged.		
1	Insulin	Remission, then relapse	Insulin	Remission maintained
1	Insulin	Remission, then relapse	Electroshock & insulin	Patient improved & discharged
3	Electroshock & insulin	Remission maintained		
1	Electroshock	Remission, then relapse	Electroshock & insulin	Remission maintained
1	Electroshock	Remission, then relapse	Insulin	Remission maintained
1	Electroshock	Remission, then relapse; repeated.	Electroshock & stilbestrol	Remission maintained

Thirty-four patients were given electroshock, ambulatory insulin and psychotherapy alone or in various combinations as the initial treatment (Tables 1 and 2). Of these, 17 were improved or went into remission that was maintained and were discharged, and 17 went into remission followed by relapse (including 1 who was discharged and then killed herself). One or more courses of similar therapy resulted in the discharge of 5 more patients. The remaining 11 were then given progesterone with or without shock therapy. Five others were given progesterone as the initial treatment with or without shock therapy. In effect the nonhormonal therapies constituted control procedures with which progesterone administration was compared.

When progesterone was given, 100 mg. was usually

*From the Clinical Services and Laboratory of Clinical Physiology, McLean Hospital, and the departments of Psychiatry and Medicine, Harvard Medical School.

†Assistant in psychiatry, Harvard Medical School; chief, Women's Service, McLean Hospital.

‡Assistant clinical professor of medicine, Harvard Medical School; director of internal medicine and research in clinical physiology, McLean Hospital.

administered intramuscularly every day for about ten days; it was then given orally in doses of 150 mg. a day. After the patients were discharged from the hospital some continued to receive the hormone by mouth, for periods ranging from a few weeks to many months.

Observations

Inspection of Tables 1 and 2 shows that post-partum psychosis, which a generation ago was a dread disease, now usually terminates in recovery when treated by modern methods. Electric-shock treatment is usually followed by remission; this, however, is often only temporary, since relapse frequently occurs when the treatment is stopped. This is true of other forms of therapy when they are administered without progesterone; 17 of the subjects of this study who went into remission without having received progesterone later underwent one or more relapses. This represents an over-all relapse rate of 17:39, or 43.6 per cent. If patients who went into remission only while receiving progesterone are excluded, the relapse rate for all other therapies is increased to 17:34, or 50.0 per cent.

By contrast, the rate of relapse in patients who received progesterone while undergoing remission or during relapse after other therapy was 1:16, or 6.3 per cent. This strongly indicates that the administration of progesterone works toward the retention of a remission achieved by means of other therapy or the establishment of remission after relapse that followed other therapy. No other combination of treatments showed any consistent outcome.

It is to be noted that progesterone alone did not usually effect a remission. The hormone alone did appear to induce remission after relapse that followed electric shock, even when given without additional electric shock. Progesterone sometimes worked together with insulin toward achieving or maintaining a remission. The outstanding result, however, was that, with 1 exception, it regularly induced lasting remission in combination with electric-shock treatments, usually 5 to 7 in number.

Follow-up information has been obtained concerning most of the patients who received the hormone. Information on these patients covers the following lengths of time: 1 patient for five years; 1 for four years; 2 for three years; 1 for two years; 4 for one year; 3 for four to six months; 1 for one month; and 2 patients, no information. None of the successfully treated patients have been known to have a recurrence of psychosis. Three patients are known to have given birth to one more child each without untoward event.

Table 2. *Results in Patients Treated with Progesterone.*

Case No.	Initial Treatment	Result	Later Treatment	Result
1	Electroshock & insulin	Remission, relapse, then no improvement	Progesterone	Remission maintained
2	Electroshock & insulin	Remission, then relapse	Insulin & progesterone	Remission maintained
3	Insulin, then insulin & electroshock	Improvement, then relapse, twice	Progesterone	Remission maintained
4	Electroshock & insulin	Remission, then relapse, twice	Electroshock & insulin; progesterone.	Remission, then relapse, twice
5	Psychotherapy	Remission, then relapse	Electroshock & progesterone	Remission maintained
6	Electroshock	Remission, then relapse, twice	Electroshock & progesterone	Remission maintained
7	Electroshock, then insulin, then electroshock	Remission, then relapse, 3 times	Progesterone	Remission maintained
8	Electroshock	Remission, then relapse, 4 times	Progesterone	Remission maintained
9	Electroshock	Remission, then relapse, twice	Progesterone	Remission maintained
10	Electroshock & insulin	Remission, then relapse	Progesterone	Remission maintained
11	Insulin	Remission, then relapse	Progesterone & insulin	Remission maintained
12	Insulin & progesterone	No improvement	Electroshock & progesterone	Remission maintained
13	Insulin, electroshock & progesterone	Remission maintained		
14	Insulin, electroshock & progesterone	Remission maintained		
15	Progesterone	Remission maintained		
16	Electroshock & progesterone	Remission maintained		

Selected Case Reports

Case 1. A 26-year-old woman, who had given birth to her 2d child on June 24, 1953, was admitted to the McLean Hospital on July 22, 1953, because of agitated behavior of 12 days' duration developing into excitement and delusions, including the belief that her father was dead.

On admission she was found to be mentally confused and aimless in much of her behavior; she entertained strange ideas about her family and had auditory hallucinations. She was given a course of electric-shock treatment between July 27 and August 10, with marked improvement. Within a few days of the cessation of electric shock she went into relapse, having depressive symptoms and fearing that her husband might be dead. Electric-shock treatments were resumed, 26

being given between August 19 and September 29. In addition, a course of insulin was given on an ambulatory basis between August 4 and September 23. During the 2d course of electric-shock treatments the patient improved moderately for a time but later became confused, whiny, resistive and alternately mute and incoherent. She was given progesterone intramuscularly in daily doses of 100 mg. beginning on September 23 for 4 days; thereafter she received 150 mg. a day by mouth until October 14. By October 6 she had shown distinct improvement, and she continued to improve steadily until her discharge on October 15. Follow-up information obtained in May, 1955, indicated that she had remained well after leaving the hospital and that she had cared for her children competently.

CASE 2. A 24-year-old woman who had given birth to twins on November 9, 1953, was admitted to the hospital on December 12, 1953, because she had been depressed for 1 week; because on the day before admission she had thought that her husband was sending gas through the house by way of the radiator system and that her voice was being recorded; and because she said she wanted to kill herself. She had become pregnant only after gynecologic intervention, including tubal insufflation. Pregnancy had been marked by the fact that she was surprised to learn that she was going to have twins (which had caused her husband to become angry at her obstetrician!).

The patient was a well educated woman, ordinarily known to be sociable, vivacious, pleasant and intellectually active. She had been happily married for 2 years.

In the hospital she was found to be co-operative but depressed and confused in her thinking; she believed that she might be in love with the physician interviewing her and sometimes believed herself to be a hermaphrodite. Shortly after admission she became mute and impulsive. Throughout the hospital course she was given intensive psychotherapy. In addition, she received 8 electric shocks between December 21, 1953, and January 7, 1954; she was also given insulin therapy on an ambulatory basis between December 16, 1953, and January 11, 1954. She seemed symptomatically recovered by about December 29. However, by January 21 she showed definite symptoms of relapse, being tense, fearful, withdrawn, and confused in her thinking. Progesterone, 100 mg. a day intramuscularly, was started on January 22, and insulin on an ambulatory basis was reinstituted on January 26 and continued through February 19. By January 27 she was much better, and thereafter she progressed rapidly to symptomatic recovery. She was discharged from the hospital on February 26, and continued to take progesterone, 150 mg. a day by mouth, for several months. Follow-up information received in May, 1955, indicated that she had remained very well.

CASE 3. A 24-year-old woman gave birth to a child in December, 1951. She soon manifested symptoms of serious psychiatric illness, becoming depressed, suicidal and assaultive toward her baby. Symptoms continued in greater or lesser degree, and after a suicide attempt early in 1953 she was admitted to another hospital, where she was given insulin-coma treatment. She did poorly and was given electric-shock and further insulin-coma treatment during the first 5 months of 1954. Her subsequent progress was so unsatisfactory that lobotomy was considered, but this was not carried out. Instead, at our suggestion, a trial of progesterone alone was made for 2 months during the summer of 1954. She improved dramatically while under this treatment and was discharged to her home; this improvement has continued during the past year.

CASE 4 (failure to recover). A 30-year-old woman was admitted to the McLean Hospital on April 6, 1950, because of delusions and disturbed behavior of 3½ years' duration. After the delivery of her 1st child in 1940 she had become psychotic, and this condition had persisted for 2 years, after which she improved. She gave birth to a 2d child in 1946, and soon afterward became first suspicious and then highly disturbed. Between 1946 and 1950 she was admitted to several other hospitals in succession, where she was given courses of electric-shock and insulin treatment but relapsed in each instance. Further electric-shock treatment was given shortly after admission to the McLean Hospital. Progesterone, 100 mg. a day intramuscularly, was given from the end of April to July, 1950, and again between September and December, 1950. No improvement resulted, and she was transferred to another hospital, where lobotomy was later performed.

DISCUSSION

Available physiologic data are inadequate to explain the beneficial clinical results of the treatment of post-partum psychosis with progesterone. Further study of the endocrinologic changes of pregnancy and the puerperium should be made, both in women who become psychotic during the puerperium and in those who do not.

There are marked changes in adrenal function during pregnancy and in the early post-partum period. A decrease in the blood eosinophil count occurs in pregnancy.[3-5] The blood[6-8] and urinary[5,9,-10-13] steroid contents are increased in normal pregnancy, rising to about seven times the normal level immediately after delivery[8] and perhaps even higher in primiparas[14]; the blood corticoid concentration returns to normal on about the sixth day post partum. The ACTH made by the placenta[11,15-19] probably causes the adrenocortical hyperactivity that occurs in pregnancy; the data of Böe and Salvesen,[20] who found no ACTH in the placenta, are discordant. Whether or not the placenta also makes corticoid hormones is still in dispute.[15,21,22] It is probable that the large amount of progesterone made by the placenta tends to depress maternal adrenocortical function; at least observations in rats[23,24] and in man[25] show that exogenous progesterone has this effect. Presumably, the placental ACTH counteracts this phenomenon. The termination of pregnancy, with the loss of the placental ACTH and the concomitant loss of the depressing effect of progesterone on the adrenal cortex, constitutes a period in which rapid and marked readjustments of pituitary-adrenocortical function must occur.

A hypothesis thus suggests itself: progesterone made by the placenta depresses the anterior pituitary gland and thereby the adrenal cortex; on the other hand, ACTH produced by the placenta directly stimulates the adrenal cortex. (Well known clinical indications of adrenocortical hyperactivity in pregnancy are the amelioration of arthritis, the euphoria and possibly the psychoses developed during this period.) The post-partum loss of the placenta, with the consequent loss of the ACTH-produced stimulus to adrenocortical overactivity, may account for the frequently observed loss of euphoria that takes place on about the fourth day after delivery.

The concomitant loss of progesterone, on the other hand, may perhaps be later followed by a rebound of the anterior-pituitary function and hence a restimulation of the adrenal cortex. This change, if excessive, might contribute to the development of post-partum psychosis.

The patients studied here exhibited behavioral

changes severe enough to necessitate hospitalization. Most of those who improved while on progesterone therapy received some shock treatment also; a few improved on progesterone therapy alone. Further study may reveal that patients who show milder changes require only the hormone. A trial of progesterone therapy should be made in women who have either incipient psychotic symptoms or a severe increase in neurotic symptoms after the first week post partum.

No evidence has been accumulated that indicates how long progesterone should be given, or even the total amount needed. It seems advisable to continue the administration for at least three weeks. The hormone should be withdrawn gradually, and if the symptoms recur the dose should be increased to its original level.

The use of progesterone in other early psychoses in women should be studied further. There are indications that it may be beneficial in some cases.

Summary

Thirty-nine hospitalized patients with post-partum psychosis were studied. Progesterone in large amounts was used in the treatment of 16 of these, most of whom had gone into relapse after remissions achieved by other somatic methods. They included patients treated by various combinations of psychotherapy, insulin and electric shock. When progesterone was given it was used alone or in combination with other therapy. The data show that remissions achieved without concurrent administration of progesterone were often temporary whereas remissions achieved while progesterone was being administered were lasting (the 1 exception being a patient who had been psychotic for the greater part of seven years before receiving the hormone). The use of progesterone increased the remission rate in post-partum psychosis to almost 100 per cent.

References

1. Altschule, M. D. *Bodily Physiology in Mental and Emotional Disorders*. 228 pp. New York: Grune & Stratton, 1954.
2. Altschule, M. D., and Tillotson, K. J. Use of testosterone in treatment of depressions. *New Eng. J. Med.* **239**:1036-1038, 1948.
3. Davis, M. E., and Hulit, B. E. Changes in circulating eosinophils in women during menstrual cycle and reproduction. *J. Clin. Endocrinol.* **9**:714-724, 1949.
4. Bernstine, J. B., and de Andino, A. M. Studies on circulating eosinophils in normal and toxemic pregnant women. *Am. J. Obst. & Gynec.* **63**:181-183, 1952.
5. Schoen, I., and Schnall, D. Eosinophil and urinary corticoid changes as related to pituitary-adrenal-like function in pregnancy. *Surg., Gynec. & Obst.* **98**:161-168, 1954.
6. Lloyd, C. W., Hughes, E. C., Lobotsky, J., Rienzo, J., and Avery, G. M. Some hormone studies in normal and toxemic pregnancy. *J. Clin. Investigation* **31**:1056-1063, 1952.
7. Christy, N. P., Wallace, E. Z., and Jailer, J. W. Effect of intravenously-administered ACTH on plasma 17, 21-dihydroxy-20-ketosteroids in normal individuals and in patients with disorders of adrenal cortex. *J. Clin. Investigation* **34**:899-906, 1955.
8. Lemmel, C. A. Blood levels of 17-hydroxycorticosteroids in normal pregnancy. *J. Clin. Endocrinol.* **13**:898-902, 1953.
9. Venning, E. H. Adrenal function in pregnancy. *Endocrinology* **39**:203-220, 1946.
10. Tobian, L., Jr. Cortical steroid excretion in edema of pregnancy, pre-eclampsia and essential hypertension. *J. Clin. Endocrinol.* **9**: 319-329, 1949.
11. Jailer, J. W., and Knowlton, A. I. Simulated adreno-cortical activity during pregnancy in Addisonian patient. *J. Clin. Investigation* **29**:1430-1436, 1950.
12. Parviainen, S., Soiva, K., and Vartianen, S. Corticosteroid excretion during pregnancy, especially in toxemia of late pregnancy. *Acta obst. et gynec. Scandinav.* **29**: Supp. 5, 1950.
13. Hills, A. G., Venning, E. H., Dohan, F. C., Webster, G. D., Jr., and Richardson, E. M. Pregnancy and adrenocortical function: endocrine studies of pregnancy occurring in two adrenal-deficient women. *J. Clin. Investigation* **33**:1466-1480, 1954.
14. Gemzell, C. A. Variations in plasma levels of 17-hydroxycorticosteroids in mother and infant following parturition. *Acta endocrinol.* **17**:100-105, 1954.
15. Opsahl, J., and Long, C. N. H. Identification of ACTH in human placental tissue. *Yale J. Biol. & Med.* **24**:199-209, 1951.
16. Tarantino, C. Sulla presenza di ACTH nella placenta. *Folia endocrinol.* **4**:197-201, 1951.
17. Cohen, H., and Kleinberg, W. Placental content of A.C.T.H. *Lancet* **2**:201, 1952.
18. Sulman, F. G., and Bergmann, F. Adrenocorticotrophic activity of placental extracts. *J. Obst. & Gynaec. Brit. Emp.* **60**:123-125, 1953.
19. Assali, N. S., and Hamermesz, J. Adrenocorticotrophic substances from human placenta. *Endocrinology* **55**:561-567, 1954.
20. Böe, F., and Salvesen, S. Placental content of A.C.T.H. *Lancet* **1**:1210, 1952.
21. Venning, E. H., Randall, J. P., and Gyorgy, P. Excretion of glucocorticoids in newborn. *Endocrinology* **45**:430-434, 1949.
22. Johnson, R. H., and Haines, W. J. Extraction of adrenal cortex hormone activity from placental tissue. *Science* **116**:456, 1952.
23. Clausen, H. J. Atrophy of adrenal cortex following administration of large amounts of progesterone. *Endocrinology* **27**:989-993, 1940.
24. Selye, H. Compensatory atrophy of adrenals. *J.A.M.A.* **115**:2246-2252, 1940.
25. Hamburger, C., and Sprechler, M. Influence of steroid hormones on hormonal activity of adenohypophysis in man. *Acta endocrinol.* **7**:167-195, 1951.

SPECIAL ARTICLE

IN A LIFETIME*

Irving J. Walker, M.D.†

BOSTON

IT is natural for an audience to assume that one who has survived beyond the Biblical age of three score years and ten might touch upon a few changes in professional activities during a lifetime that by chance includes that period referred to as the "Golden Age of Medicine." In so doing I shall risk being relegated to the lowly status of "the Old Dr. Chips" in Dunphy's[1] classification. There is no intent on my part to be either soothsayer or reformer. My generation of surgeons is indeed grateful to have served during a time when the doors hiding the secrets of disease have been so widely opened by medical progress.

*Abbreviated from the Presidential Address, delivered at the annual meeting of the New England Surgical Society, Bretton Woods, New Hampshire, September 16, 1955.

†Clinical professor of surgery, emeritus, Harvard Medical School; consulting surgeon, Boston City Hospital.

Antiseptic Surgery

After debates over its merits, both here and abroad,

during the seventies and eighties of the last century, it was ordained that antiseptic surgery, conceived in Scotland, opposed in England but meticulously practiced in Germany, was to be accepted indifferently and sporadically in the United States. Here the faithful followers of Lister, as recorded by Halsted, "contended with prejudice and parried the almost venomous thrusts of the skeptical and the envious." Unfortunately, some of the envious were all-powerful characters in the field of surgery, whose influence weighed heavily against Listerism. Incidentally, the Brahmins among ultraconservative Boston surgeons, even as late as 1881, could have stolen the antiseptic show for their Hub of the Universe if they had been united in accepting the recommendation of Henry O. Marcy, a pupil of Lister, who in that year, according to Cushing,[2] "was almost the only ardent advocate of antiseptic surgery in Boston." His recommendations not being accepted, Marcy, his enthusiasm temporarily dampened, withdrew to his bailiwick in Cambridge, there to pursue the study and practice of antiseptic and later aseptic methods — somewhat of a martyr to a cause. The green-eyed monster again had reared its ugly head. There is always a hazard for the pioneer in theory, particularly if he is overzealous in espousing his cause.

The beginning of the end of the precarious life of antiseptic surgery came with the scientific application of heat in the form of steam sterilization of dressings by Schümmelbusch in 1885 and the boiling of instruments by Davidsohn in 1888, both examples of German contribution to medical science. In Boston, states Cushing,[3] "not until 1892 did C. A. Porter and Franklin Balch, as internes, purchase for the hospital [Massachusetts General] its first Arnold sterilizer." The aseptic era was here.

Aseptic Surgery

Forthwith, the carbolic spray went to the trash heap, grudgingly discarded sea sponges were replaced by those of gauze, and the much beloved, blood-stiffened frock coats were relegated to the fire — a veritable surgical housecleaning. Sterile gowns of white presently appeared. Bearded faces of operators, gradually yielding to the razor, occasionally were masked. Soon, white caps, esthetically covering bald pates, accorded distinctive halos to the wearers. Even the hands, having been subjected to removal of more than superficial grime by the liberal use of water and abused by harsh soap and strong antiseptics, were first encased in the cotton gloves of Mikulicz and, beginning in 1890, in those of rubber, a contribution of Halsted to asepsis. Nor was the patient exempt from the enthusiasm of aseptic technic. Earmarks of the razor of questionable cutting quality left no doubt regarding the portion of the anatomy that had been elected for surgery. The half-naked body of the patient of the early antiseptic era came to be draped in sheets of white. The first glimpse of such a setting must have impressed the more religious of the eager observers with the similarity to the situation, expressed in the words of an old hymn, "Wash me and I shall be whiter than snow."

Science and Specialization in Surgery

Surgical amphitheaters of the nineties with surgeons, assistants and nurses in the roles of actors were the scenes of glamorous performances, the beginning of the present era of almost incredible surgical accomplishments. Surgery had welcomed physical science to its fold. It was not by chance that the application of science to surgery coincided with its employment in industry, nor is it surprising that this development marked the beginning of a rising tempo of human competition for materialism. Unquestionably, science must continue to be cultivated to the utmost, but its contributions should be so assimilated in daily living as to produce a moral and spiritual uplift to all mankind rather than strife among the recipients of its benefactions.

Looking backward to the relatively quiescent nineties, one discovers the acceptance of surgery as an additive to the restoration of health rather than as a last resort for the preservation of life. Surgery as a specialty then was born, and with it came its recognition as such in undergraduate medical education and graduate training of surgical interns and the occasional resident. From among this group came the teachers of many. Not academic, as this term is now used, those clinicians deserve much credit for their enthusiasm in endeavoring to integrate science with their inherent empiricism, at the same time cultivating the qualities of gentlemen.

In the year 1889-1890, there came quietly into being at Johns Hopkins Hospital a school of surgical philosophy, guided by William S. Halsted, the aspirations of which have been abundantly fulfilled. Its original disciples figuratively sowed the seeds of a future forest of dedicated teachers and perfectionists in the practice of surgery. Their clear-cut perception of the value of science as a basis of the ultimate in the surgical treatment of disease and trauma contributed immeasurably to a new approach in medical education that culminated in the Flexner report of 1910. In medicine, as in all science, specialization within specialties has become the order of the day. Current comment to the contrary, such specialization bids fair to continue and even to expand, if for no other reason than that there must be some limitation to the amount of knowledge that the individual brain can assimilate.

Surgery and the Hospitals

Public recognition of the value of aseptic surgery necessitated accommodations for an ever-increasing hospital population. Although hospitals had been founded primarily for the indigent sick, the middle-income class of the nineties was not slow in conclud-

ing that they had become institutions for recovery rather than havens for the demise of the poor. Hence, in cities, large and small, a wave of hospital construction got under way during the last decade of the nineteenth century. However, for some years the conservative well-to-do class refrained from mingling with their plebeian fellows in illness; choosing, when necessary, to convert their homes into sick rooms. This short-sighted policy yielded to one that brought forth private hospitals solely for the wealthy, which as such have long since disappeared. By 1910 it was apparent, except for city, state, federal and certain denominational institutions, that for efficiency and economy a portion of existing hospitals and of those to be built should incorporate accommodations for all income groups under one management. Consummation of these plans brought about the present concept of allocating bed space for all classes in the modern voluntary hospital.

Hospital Economics

The phenomenal growth of science in the treatment of disease has become a complication of institutional economics. Accompanying the present high level of medical efficiency with elaboration of hospital accommodations, equipment and services, the public complaint of the high cost of institutional care, justifiably or not, remains an unsolved problem. Until forty years ago the cost of illness, always unpopular, actually was a trivial matter in the social economy. The intricacies of inflation were at that period nonexistent, taxes were not burdensome, and unwarranted spending for luxuries was restrained. Medical costs never were and never will be a concern of the poor. Charity and taxation rightfully assume this obligation. Nor were the wealthy the least interested in this phase of living cost until increasing taxation effected a siphoning off of acquired and inherited income, some of which funds formerly were diverted to medical charity. The savings of the proud middle class provided for the exigencies of sickness. Inflation and the forty-hour week are well known to be the chief factors that have adversely affected institutional economy.

No one will disagree with the statement that voluntary hospital activities constitute "big business," limited, however, by the necessity of its being profitless, thus producing a difficult financial situation with which trustees, management and medical staffs all must be concerned. Over the past quarter of a century physician influence in hospital affairs has markedly diminished, staff prerogatives having been encroached upon by administration. Granting that medical staff power of years ago created abuses that necessitated curbing, is it not possible that the trend has swung too far in the other direction, and that present staff-trustee relations, including management, deserve reappraisal? There could be an advantage of incorporating in the governing bodies of hospitals one or more recently retired or senior staff members, preferably the former. The number should constitute not more than 25 per cent of the board. These appointments should be accepted only as opportunities for furthering hospital efficiency, without frills in accoutrement and manpower, at the lowest possible cost to the patient. The expense of hospital care being high and rising, it is essential that physicians devote more thought to what extent in the situation they may unwittingly be playing a part. In their academic approach to disease they are likely to overlook the practical aspects of the costs involved. To offset this tendency the matter of unnecessary hospitalization warrants more thought. Within such institutions nonessential studies in diagnosis and overindulgence in the ramifications of treatment deserve greater individual attention.

Ethics and Medical Practice

All has not been well with the ethical practice of medicine. The malefactions of comparatively few within the profession have reflected on the honesty and integrity of the many who have unselfishly maintained the ideology of service rather than profit. Physicians should be grateful to their fellows who have recently had the fortitude to face the issue squarely in dealing with a distressing situation. However, there are those who blithely make light of the frequency and importance of deviations from ethical standards. The philosophy of this group overlooks the unfavorable potentialities attendant on interjecting certain undesirable commercial customs aimed at profit into a profession dedicated fundamentally to service, in which monetary reward should be a necessary but secondary consideration.

Again, to help preserve the heritage of idealism, would it not be well if physicians of the present era periodically gave some impartial self-scrutiny to the comparative priority rating of individual aims — namely, whether they are those of service or those of profit? From these appraisals, and with the recollection that no man can serve two masters, one's conscience remains the guide to conduct.

Costs of Medical Care

The tenets of rugged individualism and thrift, as well as the national economy, were dealt a staggering blow by extravagant exhortations and revolutionary legislation initiated nearly a quarter of a century ago. Since then the proponents of governmental paternalism have so multiplied and become so indoctrinated by experience that the pattern of private enterprise is being severely tested. What a difference from the philosophy of a nation born into independence, reared on hard work and thrift, where personal debt was a disgrace and any question of governmental solvency was viewed with misgivings!

The issue of socialized medicine is ever present.

With the members of the profession recorded against such an issue, their house must continuously be well ordered and they must be united, assertive and persuasive since the public will continue to scrutinize their activities from the point of view of future Government support and, *ad eundem,* the regulation, if not the control, of medicine.

The measurements of the profession's contribution to the welfare of society are being judged on the variables in the grade and cost of medical care. Although the quality of current endeavors is generally extolled the charge that medical care is excessive in cost has been loosely heralded.

After all the discussion of social, economic and political issues by physicians, administrators and governing bodies of hospitals, as well as insurance interests, does not the public remain inadequately informed regarding the conclusions? If so, would it not be desirable for an authoritative body representing the parent organizations of these groups to co-ordinate the respective conclusions and recommendations and transmit them to the public in language easily understandable and through channels that would attract the widest attention? Ought not the public, by diplomatic approach, be educated to the realization that some of the complaints of the high cost of living, including certain aspects of sickness, should be interpreted as the cost of high living, when, in fulfillment of their ambitions and encouraged by the liberality of credit, too many have been buying more than they could afford?

When bills for illness become a financial catastrophe it is too late to grieve over what might have been mitigated or avoided by previous savings through restraint in spending. Should not all legitimate persuasion be exercised toward convincing the laity that sickness, not referable to public health, is a phase of life whose cost should be individually assumed as a necessity and at present best provided for by a backlog of continuous savings in addition to the funds yearly allocated for the most comprehensive forms of sickness insurance?

Finally it might be added that the easy way of compromising with the menace of compulsory health insurance by enlarging the present scope of federal grants-in-aid for individual medical expenses would have expanding possibilities with adverse repercussions on the future of voluntary medicine.

"Charity in the literal sense and in the form of alms dispensed by Lady Bountiful may disappear from the American scene but the medical profession would do well to treasure such vestiges of it as remain," said E. D. Churchill[4] reaffirming the Biblical statement that "Man doth not live by bread alone." By inference one may assume that materialism of itself does not fulfill man's quest for happiness and that to achieve such an end he must attain a spiritual idealism.

Materialism and Service to Mankind

Human beings were placed upon this earth presumably for two purposes: to propagate the species and to serve mankind, the latter with the precept of the spoken word or documental religion as a guide to conduct. As of today these assumptions are an oversimplification of our way of life.

Of these premises I am here concerned only with sociology — particularly with the aspect of it that pertains to man's reciprocal service to his fellows. The male of the species early discovered that food, shelter and covering for the body were necessities of existence for himself and his family. The search for and elaboration of these materials brought men into conflict with one another — the beginning of some present problems in social relations. However, conflicts among aborigines, with resulting injuries to the participants, developed latent instincts in the care of the wounded, both friend and foe alike, as a demonstration of subconscious humanitarianism. And so one sees the life of early man, even as of today, singly and collectively involved in a duel of antagonistic purposes: an increasing competition for materialistic gains versus the instinctive impulse to serve the less fortunate in health and worldly goods. A proper balance between these motivating forces has ever been difficult to maintain.

Humanitarianism and Humanism

In recent years the modus operandi seems to have become an increasing struggle for the economic survival of the fittest, with a selfish attitude toward the less aggressive competitor who may be equally or even more humane. During the same period scientific investigation in a highly competitive and intensive phase has predominated over humanism, particularly as the latter is applied to mental cultivation as one approach to humanitarianism. Granted that science is factual and lacking in emotion, is there any reason why scientists should not profitably indulge in the cultures and in turn humanists discover new horizons by musing in the fields of science? Possibly, the present concept of the behavioral sciences with an added humanistic flavor would promote a common interest and thereby tend to narrow the gap currently existing between the objectives of the scientists and the aims of the humanists. Might not this interest center around an even better understanding of the evolution of man and his environmental reactions of the past and present with meditation upon his future?

As viewed from beyond the shadows of the Halls of Ivy one is led to conclude that one's academic brothers have been themselves disturbed about what disciplines should constitute the behavioral sciences and consequently are somewhat confused concerning their application in teaching.

There is evidence that the tide has recently turned

and that history is about to repeat itself in re-emphasizing the importance of humanism in education. As applied to the medical profession the literature suggests that, without belittling the physician's debt to science and his future expectations from it, he might profitably review what his predecessors gained from humanism, and what he, in turn, has been losing by slighting the humanities. But as a profession why should doctors be too concerned with the cultures when through science their end results have reached far beyond the realm dreamed of only two generations ago? The answer should be that, regardless of occupation, all share equal responsibilities in promoting humanitarianism, one product of humanistic study. If, in accenting the sciences with neglect of the humanities, society is, through competition, producing a strain of triggered mentalities subject to functional and psychosomatic diseases, what is the human race gaining? Also, when science can be utilized to disrupt nations spiritually, as in the past, and in the future can be diverted to total physical destruction, what has the so-called civilized world acquired? From these, certainly, not the moral virtues of humanitarianism. If physicians indulged more in humanism would they not be better prepared to understand themselves and thereby better qualified to serve their patients psychologically as well as physically? Of even greater value could be their examples in elevating the general quality of citizenship.

It has been a long time since the remaining classical libraries of the well-to-do have been disturbed. Where they exist they are retained apparently for ostentation or treasured as reminiscent of an age of gracious living. Bookcases and their contents in the living rooms of the middle class have been replaced by television sets substituted as sources of entertainment and not education. I trust that most adults still cherish the lasting impression made upon them as youngsters by parental reading of fascinating episodes from the illustrated Bible and likewise the stimulus from children's classics. But, to borrow from Elkin,[5] "What can we expect when easy transportation, the movies, television, gin and gin rummy have largely replaced the home and the church as a social and educational forum."

Grade schools, in stressing local and national history, effected a sort of hero worship of statesmen and generals in their services to the country and supplied an incentive to future study of the humanities by adolescents. As of the present, once again with a reference to Elkin[5]:

> Secondary schools which were once the bulwark of classical learning have become largely a sort of trade school, and where once Latin, Greek and English literature were taught we find extensive courses in agriculture, homemaking (including cooking) and various handicrafts (including automobile and tractor maintenance). The colleges have said requiem over Greek, which is as dead as a dodo, and Latin is rapidly on the way to join the passenger pigeon and the New England Heath Hen.

It is perhaps illogical to anticipate that the present adult population can be re-educated to the virtues of humanism, but is it not possible that their offspring could profitably be guided along these lines? With more leisure, more wealth, classical literature and the facilities of radio and television all available, it is apparent that only the motivation of adult influence is lacking to further the value of humanism in youth. So far as the relative worth of the humanities versus the sciences in medical education is concerned I can only refer to more authoritative sources. Osler,[6] in 1904, realizing the value of classical literature in undergraduate medicine, made the following recommendation:

> A liberal education may be had at a very slight cost of time and money. Well filled though the day be with appointed tasks, to make the best possible use of your ten talents rest not satisfied with professional training but try to get the education if not of a scholar at least of a gentleman.

To this end he listed ten books for leisurely reading, starting with the New and Old Testaments and ending with the *Breakfast Table Series* of Oliver Wendell Holmes. These directives of inspiration and wisdom could profit the laity as well as the medical profession. At present, in stressing humanism, many have agreed that re-emphasis upon the cultures, with somewhat lessened concentration upon the sciences in colleges, should, at the completion of a medical-school career, produce an upgrading of the qualities of good citizens, understanding physicians and dedicated teachers,—goals not without merit—and examples of progress to other professions, scientists, industrialists and tradesmen.

Finally, it is well to recall that the finer qualities of instinctive humanitarianism are enhanced by daily practice and are not completely satisfied by occasional monetary philanthropy, important though that may be. In short, the dollar will never represent the optimum of man's contribution to the welfare of his brothers.

Conclusions

One may deduce that over the past half-century the nation, by scientific achievements, has miraculously advanced its standards of living, including that of the care of the sick. However, in the race for worldly goods, may it not have over-run itself, thereby distorting its sense of values by overestimating the importance of materialism and minimizing the merits of the finer attributes of humanitarianism as exemplified by the Golden Rule? As for the future, "We shall see what we shall see."

References

1. Dunphy, J. E. University surgeon. *Surgery* **36**:353-361, 1954.
2. Cushing, H. One hundred and fifty years: from tallow-dip to television. *New Eng. J. Med.* **204**:1235-1244, 1931.
3. *Idem.* Personality of hospital. *Boston M. & S. J.* **185**:529-538, 1921.
4. Churchill, E. D. Address of president: science and humanism in surgery. *Tr. Am. S. A.* **65**:1-16, 1947.
5. Elkin, D. C. Case for study of humanities in making of doctor. *Tr. Am. S. A.* **70**:1-8, 1952.
6. Osler, W. *Aequanimitas: With other addresses to medical students, nurses and practitioners of medicine.* 389 pp. Philadelphia: Blakiston, 1904.

MEDICAL PROGRESS

CURRENT STATUS OF THE CLINICAL USE OF ANTIBIOTIC-VITAMIN COMBINATIONS*

GRACE A. GOLDSMITH, M.D.†

NEW ORLEANS, LOUISIANA

THE therapeutic value of antibiotics in many of the heterogeneous infections to which man is susceptible has been amply documented and does not require elaboration at this time. Recently, the suggestion was made that administration of vitamins in combination with antibiotics may prove more beneficial than antibiotics alone. The "therapeutic vitamin formula" that has been used in combination with antibiotics is the one tentatively suggested in the bulletin *Therapeutic Nutrition,* which was prepared with the collaboration of the Committee on Therapeutic Nutrition of the Food and Nutrition Board of the National Research Council and published in 1952.[1] The conjectural nature of this report was indicated in the text as follows: "The recommendations concerning nutritional requirements for the various disease states covered by this report are based on the limited knowledge available at present and should be considered tentative pending further research results." The Food and Nutrition Board recently decided to withhold further printing and distribution of this report pending critical reconsideration of the subject.[2]

Whenever a new or modified therapeutic procedure is suggested, it is desirable to consider, first, the rationale for such therapy and, secondly, the efficacy of the new treatment in comparison with that used previously. It appears reasonable to administer vitamins in combination with antibiotics in the treatment of infections, if any of the following hypotheses can be substantiated: "optimal" vitamin nutrition or the administration of certain vitamins increases host resistance to specific infections; specific infections increase the requirement or decrease the utilization of vitamins; antibiotic administration increases the need or adversely influences the utilization of specific vitamins; or administration of vitamins favorably influences the action of antibiotics per se. Final evaluation of the efficacy of combined therapy with vitamins and antibiotics will, of course, be dependent on demonstration of greater efficacy of the combination than of antibiotics alone. There is some information, although far too little, bearing on each of these hypotheses suggested.

Discussion of the problem under consideration involves the whole field of relations between nutrition and infection, a field of great importance in which considerable investigation has been done but from which little clear-cut information has been obtained.

INFLUENCE OF VITAMIN NUTRITION ON RESISTANCE TO INFECTIONS

In 1949, Clark et al.[3] stated that clinical observations and general impressions suggest that optimum nutrition commonly aids resistance, but knowledge is too meager for optimum nutrition to be defined and knowledge of factors involved in resistance seems even less complete. In spite of advance in knowledge in the past six years, this statement still holds true. In a recapitulation of papers presented at a recent symposium on nutrition and infection, Schneider[4] commented: "it is now more obvious than ever that there is no clear and simple connection between infection and nutrition that has won universal assent." This statement applies to the relation of vitamins to resistance to infection.

Most of the studies dealing with vitamins and resistance to infection have been conducted in laboratory animals rather than in man. Many of them are open to severe criticism of the plan and conduct of the investigation and interpretation of findings. It is difficult to summarize the current state of knowledge, but it appears to be somewhat as follows:

> The bulk of evidence indicates that deficiency of certain vitamins is associated with increased resistance to viral infections although decreased resistance has been reported in a few instances.[4,5]
>
> Most of the studies of vitamin deficiency and bacterial infections suggest that deficiency is associated with decreased resistance to infection.[3,6] However, many of the experiments are not convincing, and conflicting results have been obtained.[5] A few reports indicate that vitamin deficiency failed to influence, or even increased the resistance to, bacterial infection. In man, many studies have indicated that the incidence of tuberculosis is increased under conditions of severe undernutrition or malnutrition. In a recent investigation,[7] findings suggested that clinical tuberculosis developed more frequently in persons in whom concentrations of vitamins A and C in the blood were low than in persons in whom concentrations were average or high. Suzman[8] recently stated that, in his experience, persons with frank deficiency dis-

*Presented at the Third Annual Symposium on Antibiotics, Washington, D. C., November 3, 1955.

Adapted from a chapter with the same title in the forthcoming volume of *Antibiotics Annual,* by permission of the editor, Dr. Henry Welch.

†Professor of medicine, Tulane University of Louisiana School of Medicine.

ease, such as pellagra, are not particularly susceptible to infectious disease and are able to combat it at least as well as normally fed subjects.

Deficiency of certain vitamins has been shown to lower resistance of certain animal hosts to certain helminthic and protozoal infections.[2,9] In other reports, deficiency has seemed to be without effect or to enhance resistance to such infections. Epidemiologic studies suggest that nutritional factors are important in resistance of the human host to amebiasis.[9]

The studies just mentioned deal with deficiency of vitamins. There have been few investigations of the effect of administration of vitamins in excess. A recent study of *Plasmodium gallinaceum* infection in *Aedes aegypti* showed that administration of antibiotics, hormones and vitamins in the diet of the host influenced resistance.[10] Ascorbic acid increased susceptibility to infection, whereas thiamine, calcium pantothenate, niacin and biotin increased resistance. The concentration of the vitamin, or other compound administered, was a critical factor in the qualitative effect. Pyridoxine hydrochloride increased resistance when given in low concentration, and had the reverse effect when given in high concentration.

Hill and Garren[11] studied the resistance of chicks to fowl typhoid and reported a higher percentage of surviving animals and increased average survival time when high levels of vitamins were administered. When the individual vitamins were omitted from the supplement, one at a time, the effect was variable, resistance being increased, decreased or unaffected. Variance within experiments, as well as between groups, was great, and findings were not always reproducible. Wooley and Sebrell[12] stated that riboflavin or thiamine deficiency was associated with a higher mortality in experimental pneumococcal infection in mice. Administration, at the time of infection or afterward, of five to ten times the amount of thiamine or riboflavin given to control animals did not reduce the mortality.

From the findings discussed thus far, the confused state of knowledge at the present time is apparent. Several other aspects of this problem should be mentioned. Innate (genetic) resistance may be responsible for wide differences in response to various infectious agents in different animal species or even within a species.[5] There is considerable evidence that natural foodstuffs contain factors, as yet only partially defined, that seem capable of influencing resistance.[5]

Axelrod and Pruzansky[13] have conducted carefully controlled studies of the role of specific vitamins in antibody production in rats. When human erythrocytes were used as the antigen, deficiency of pantothenic acid, pyridoxine and folic acid caused severe impairment of antibody production; deficiency of thiamine, biotin, riboflavin, niacin-tryptophan and vitamin A, moderate impairment, and deficiency of vitamin D or vitamin B_{12}, no impairment. When the antigen was diphtheria toxoid, antibody synthesis was markedly impaired by deficiency of pantothenic acid, pyridoxine, riboflavin, folic acid, biotin and vitamin D; unimpaired by deficiency of thiamine and, in many cases, uninfluenced by deficiency of vitamin A. In rats deficient in pantothenic acid, administration of this vitamin had no effect on the anamnestic (booster) response to typhoid vaccine even if given after the primary response. As the authors have pointed out, the decrease in immune response in vitamin deficiency will be significant in resistance to infection only when the importance of antibodies has been established. Whether vitamin deficiencies of the degree encountered in the human population will affect antibody synthesis significantly remains to be determined.[4]

It seems obvious that many factors are involved in resistance, that resistance is specific for a given infection and that panresistance is unlikely. Geneticists have been able by inbreeding to assemble in a single host susceptibility to one disease and resistance to another. To ascertain the influence of vitamin nutrition on resistance to infection in man, it is necessary to examine specific vitamins in specific infections under controlled conditions.

Influence of Infection on Vitamin Nutrition

It is generally assumed that infections increase the requirement of most nutrients as a result of the rise in metabolic rate that accompanies fever and perhaps, also, as a consequence of physiologic changes in the tissues produced by the stress of disease. Specific data supporting this assumption are meager. Caloric requirement is undoubtedly increased in febrile illness, and it seems logical to postulate that vitamins that function in enzyme systems in the metabolism of protein, carbohydrate or fat may be needed in increased amounts. Thiamine requirement has been shown to be related to caloric intake,[14,15] and there is some evidence that this is true for niacin as well.[15,16] Similar relations have not been demonstrated for other vitamins. In hypermetabolic states such as hyperthyroidism and prolonged febrile diseases, clinical signs of vitamin B complex deficiency are encountered frequently.[17]

There is abundant evidence that infection intensifies poor nutrition. Clinicians practicing in areas in which malnutrition is common have frequently observed the precipitation of acute vitamin-deficiency disease, such as beriberi or pellagra, by an infectious process.[8] Infections are often associated with anorexia, nausea and vomiting, which limit nutrient intake. Loss of nutrients in the stool occurs when diarrhea accompanies infectious processes. Although supplementation with certain vitamins seems to be indicated in many of the situations just mentioned, there are no quantitative data on vitamin requirement under any of these conditions.

The level of vitamin A in the blood has been found to decrease during certain infections but to rise with subsidence of the infection without administration of vitamin A.[18,19] The cause of these changes has not been elucidated, nor have beneficial effects of administration of vitamin A been demonstrated. It has been shown that riboflavin is excreted when protein is being catabolized and is retained when protein is being stored.[20]

Diminution in the urinary excretion of ascorbic acid and reduction of the plasma level of this vitamin have been reported in a number of infections in man.[19] The ascorbic acid content of organs of laboratory animals suffering from certain infectious diseases has been found to be lower than that of noninfected animals.

Kinsell[21] and Ershoff[22] have recently reviewed the known effects of specific nutrients on the functional activity of the pituitary-adrenal axis in response to stress. Some of the findings appear pertinent to this discussion. As Ershoff[23] has pointed out, it is erroneous to consider that stress per se increases nutrient requirements, for stress is not a specific, unvarying entity. Nutrient needs may be increased after exposure to stress but only as a consequence of the physiologic effects of the particular stresser agent involved. An ideal diet that is optimally effective against all forms of stress is not known.

A variety of nutritional factors are concerned in both specific and nonspecific fashion with the functional activity of the pituitary and adrenal glands, as well as with the metabolic effects of corticoids.[21,22] In laboratory animals, deficiency of vitamin A, riboflavin or pyridoxine may be associated with a diminished response to stress. Thiamine deficiency appears to be associated with increased pituitary-adrenal activity. Vitamin C has a close relation to adrenal function, but the exact role of ascorbic acid remains unclear. There is some evidence that this vitamin improves utilization of cortical hormones and may decrease the requirement for ACTH stimulation under stress. However, ascorbic acid is not essential to a high level of adrenocortical function. Pantothenic acid deficiency results in histologic changes in the adrenal cortex. Although many data support the hypothesis that nutritional deficiency impairs hormone production, this hypothesis has not been established.[23] There is evidence that unidentified nutrients are required in increased amounts during stress.[22]

Kinsell[21] has suggested that "until knowledge in this field is more precise it may be well to accept the thesis that a diet is compatible with optimal ACTH-adrenal steroid production if it is high in protein, adequate in calories, moderate in carbohydrate and very adequate in ascorbic acid and members of the B complex with particular reference to pantothenic acid."

Some evidence may be cited that hormone administration may lead to vitamin deficiency.[22] Ascorbic acid excretion is increased after administration of ACTH, and hemorrhagic manifestations, presumably owing to vitamin C deficiency, have been reported. Vitamin K deficiency has also been observed after administration of large amounts of ACTH.

Available data suggest an increased requirement for vitamins in shock and anoxia.[19] Administration of large amounts of thiamine to dogs subjected to a standard type of hemorrhagic shock reduced mortality.[24] In patients who had fractures and burns, Andreae and Brown[25] found that excretion of ascorbic acid was low immediately after injury and that plasma ascorbic acid decreased even when large amounts of ascorbic acid were administered. Ascorbic acid retention was markedly increased, as demonstrated by the time required for saturation of the body with this vitamin — namely, six days, when the daily intake was 500 to 700 mg. The level of ascorbic acid in leukocytes rose much more slowly in the patients than in normal subjects who received a similar regimen. There was no evidence that the high intake of ascorbic acid was beneficial. Retention of riboflavin has been reported in the first few days after injury.[26] This period is followed by increased loss of riboflavin, balance returning to normal within about ten days. In a study of patients with injury, hemorrhage and infection, Levenson and associates[26] found low plasma ascorbic acid during fasting and after saturation tests and low excretion of thiamine, riboflavin and niacinamide, although a multiple-vitamin preparation was administered daily. Ascorbic acid excretion and plasma levels rose very slowly after ascorbic acid administration. Even patients who received large doses of vitamins excreted only small quantities in the urine until metabolic disturbances were corrected, at which time large excretions were observed. The authors interpreted the findings as indicative of increased utilization of vitamins. Because of many variables, evidence for a beneficial effect of vitamin therapy could not be demonstrated. A decrease in the level of vitamin B_{12} in serum and disappearance of this vitamin from the urine has been reported in infections.[27]

There is no doubt of the importance of maintaining adequate nutrition in infections or other stress situations. The value of nutritional therapy in diverse pathologic states — for example, tuberculosis, rheumatic fever, chronic ulcerative colitis, burns, and after surgical operations — has been established beyond question. The serious defect in knowledge is lack of precise information about nutrient needs in specific diseases. The therapeutic efficacy of large doses of vitamins, given individually or in combination, has not been determined under controlled conditions.

Influence of Antibiotics on Vitamin Nutrition

Synthesis of a number of the components of the vi-

tamin B complex and of vitamin K by the bacterial flora of the intestinal tract has been demonstrated in many animal species, and these vitamins may be used in varying degrees by the host.[28] The degree of synthesis varies with the diet as well as with the species. In man, there is some evidence for synthesis of thiamine, riboflavin, niacin, biotin, folic acid, pantothenic acid and vitamin K, but little is known about the extent of availability of these vitamins to augment dietary supply.[28,29]

In many species of animals, administration of antibiotics has resulted in growth stimulation.[30-32] This action of antibiotics appears to be mediated largely through an influence on bacteria in the intestinal tract.[32] The mechanisms involved may be destruction of micro-organisms that are deleterious to the host, changes in the flora that favor growth of bacteria that synthesize known or unknown growth factors, or inhibition of the growth of bacteria that compete with the host for some essential nutrient. There is considerable evidence for the first two possibilities, and little evidence for the third. In some experiments, the growth stimulation of antibiotics has been due to increased food intake.

Some of the antibiotics have been shown to reduce the requirement of certain animals for various vitamins of the B complex. These effects appear to be due to an increase in vitamin synthesis by the intestinal bacteria and are observed only on inadequate diets. The findings vary with the antibiotic, the diet and the animal species.

In rats, chlortetracycline administration has been found to reduce the need for vitamin B_6.[33] This antibiotic protected some, but not all, rats that received diets devoid of pantothenic acid or riboflavin from deficiency for as long as one year.[34] Penicillin, chlortetracycline and streptomycin were found to reduce the rats' requirement for thiamine, riboflavin and pantothenic acid, being most effective in rations that supplied enough of the vitamin for half maximum growth.[35] The relative effectiveness of the several antibiotics varied with the vitamin that was deficient. Orally administered chlortetracycline and penicillin increased the growth of weanling rats fed synthetic diets containing marginal levels of pantothenic acid and thiamine.[36] The antibiotics stimulated growth slightly, or not at all, with optimum amounts of these vitamins in the ration.

Oral, but not subcutaneous, administration of penicillin, chlortetracycline, streptomycin or oxytetracycline stimulated growth of rats fed diets low in riboflavin and pantothenic acid.[37] A similar effect followed penicillin and oxytetracycline when the diet was low in thiamine. These antibiotics had no growth-promoting effect in vitamin-supplemented diets. Growth stimulation was usually associated with a higher level of the vitamins in the liver and an increased urinary excretion. Administration of chlortetracycline and oxytetracycline increased the amount of niacin in the liver, and the former antibiotic enhanced urinary excretion of biotin and folic acid in rats treated with sulfonamides.[38] Penicillin was without any effect, and streptomycin appeared to increase the requirement of rats for both biotin and folic acid.

The effect of chloramphenicol on the growth of rats fed a diet deficient in pantothenic acid appeared to be dependent on the dose of the antibiotic.[39] Chlortetracycline increased the hepatic content of niacin, riboflavin, pantothenic acid and vitamin B_{12} in rats deprived of components of the vitamin B complex.[40] Penicillin stimulated growth in weanling rats fed diets free of, or low in, pyridoxine, pantothenic acid and riboflavin.[41] Chlortetracycline had a similar effect when the diet was deficient in thiamine or pantothenic acid. The type of carbohydrate in the diet influenced findings. Chlortetracycline was shown to be capable of replacing vitamin B_{12} for growth in rats fed purified diets; when antibiotic activity of chlortetracycline was destroyed, there was no growth response.[42] In the albino rat, prolonged administration of several antibiotics produced macrocytic anemia and markedly lowered urinary excretion of vitamin A, nicotinamide and folic acid.[43,44] A decrease of nicotinamide, folic acid, cobalamin and pyridoxine content of the liver was also noted.

Findings in chicks have been variable and contradictory.[32] Biely and March[45] found that the requirement of the chick for niacin, riboflavin and folic acid was reduced when chlortetracycline was added to a ration containing casein and corn. Stokstad[32] observed no evidence of a sparing action of this antibiotic on niacin, pantothenic acid, pyridoxine or folic acid in chicks receiving diets containing sucrose or glucose. Certain other antibiotics increased the folic acid content of the liver of chicks.[32] Feeding of penicillin to hens was followed by an increase in the biotin content of eggs.[32] Coates et al.[46] reported that penicillin had no effect on deficiency of thiamine, riboflavin, vitamin B_{12} or pantothenic acid in chicks but lessened the degree of biotin and folic acid deficiency and intensified niacin deficiency. In other experiments with chicks, there were no clear-cut sparing effects of antibiotics on vitamin requirement, with the possible exception of riboflavin.[30] Penicillin administration produced an increase in carotenoids in blood serum and in vitamin A in the liver.[30] Administration of chlortetracycline and diamine penicillin also increased vitamin A in the liver of chicks.[47]

There are few studies of effects of antibiotics on vitamin nutrition in man. When chlortetracycline or oxytetracycline was administered to undernourished men receiving a standard diet, urinary excretion of riboflavin increased two and a half times whereas excretion in the stool decreased.[48,49] Administration of bacitracin and polymyxin had no influence on the output of riboflavin. Marked changes in fecal flora were observed in all cases but

changes could not be correlated with other effects of the antibiotic.

Chlortetracycline or penicillin stimulated hematopoietic response when administered to patients with megaloblastic anemia in relapse.[30,31] This action may have been due to an influence on intestinal flora, resulting in increased synthesis of either vitamin B_{12}[50] or folic acid,[30] or decreased absorption of these vitamins by bacteria in the intestinal tract.

Chlortetracycline has been reported to stimulate growth in premature infants, in children receiving diets low in animal protein and in a group of mentally deficient children.[30,31] Whether the mechanism of action of this antibiotic, in stimulating growth in human subjects, is similar to that observed in several animal species remains unknown.

Serum vitamin A levels of normal men decreased after procaine penicillin injection.[51] The extent of the decrease was dependent on age, nutritional status and dosage and, in some cases, was paralleled by loss of dark adaptation. These effects were counteracted by vitamin A.

Antibiotics administered to 21 patients with infectious disease resulted in a moderate decrease in prothrombin levels in 6 patients and no change in the other 15.[12] Di Raimondo and his co-workers[53] reported a marked decrease in urinary excretion of folic acid, nicotinamide, pyridoxine and cyanocobalamin, and a lesser decrease in excretion of other components of the vitamin B complex in healthy subjects and in patients after administration of oxytetracycline, chloramphenicol and chlortetracycline. The authors stated that administration of these antibiotics to undernourished persons produced signs of hypovitaminosis.

Sarett[54] observed that oral administration of streptomycin to 6 normal subjects for eight to twenty-two days resulted in a slight fall in urinary excretion of niacin metabolites, a marked decrease in biotin excretion and no appreciable change in the output of thiamine, riboflavin or folic acid. Scuro[55] found no significant change in pantothenic acid excretion after administration of penicillin or chloramphenicol.

Local treatment of the oral cavity with penicillin may be followed by secondary infection with yeasts or molds that give the clinical picture of "hairy tongue" or "black tongue."[56] Prolonged treatment with the broad-spectrum antibiotics or with a combination of penicillin and streptomycin may lead to serious infections with *Candida albicans*.[56,57] Involvement of the mouth, pharynx, vagina and lungs is common, and fatal systemic infections have been observed. Smith[56] described a patient, treated for more than a month with chlortetracycline, in whom moniliasis of the lungs, mouth and vagina developed, together with signs suggesting pellagra — namely, disorientation, seborrheic dermatitis involving the nose and ala nasi, thickened pigmented skin over the elbows, knees and ankles, and erythema and edema of the oral and vaginal mucous membranes. Omission of the antibiotic and administration of components of the vitamin B complex were followed by improvement in the signs attributed to vitamin deficiency within ten days.

Downing[58] reported a case of black tongue that developed during treatment with chlortetracycline, the lesion healing in ten days after medication was discontinued without vitamin therapy. Krakoff et al.[59] noted severe glossitis in patients with neoplastic disease after administration of large doses of chloramphenicol. Healing occurred three to five days after antibiotic therapy was discontinued. Schulte[60] stated that soreness of the tongue and gums, which developed in 1 patient during therapy with chlortetracycline, improved after administration of large doses of vitamins, the antibiotic being continued.

Harris[61] reported that administration of chlortetracycline and chloramphenicol to patients with brucellosis was followed, often within two or three days, by a red vesiculopapular eruption on the vulva, oral mucous membrane, lips and tongue. In some patients, maceration and fissures of the oral commissures, sore throat and black tongue developed. These lesions were attributed to deficiency of components of the vitamin B complex, in spite of the rapidity of development and failure of prevention by oral administration of these vitamins. Subsequently, when components of the vitamin B complex were given parenterally each day throughout the course of antibiotic therapy, mucous-membrane lesions were said to be less frequent and less severe. *C. albicans* was isolated from the lesions in a number of subjects. Rectal, vaginal or subungual hemorrhages were noted in a few cases, but tests of blood prothrombin activity were not performed. Two subjects had dermatitis involving the areas of skin exposed to sunlight. Ellinger and Shattock[62] observed a decrease in the urinary output of nicotinamide methochloride in a patient who received oral therapy with penicillin, the output increasing when therapy was discontinued. This patient had clinical signs suggesting niacin deficiency and gave a history of pellagra several years previously. The symptoms cleared after niacinamide administration, but insufficient time elapsed before such treatment was instituted to determine the influence of withdrawal of the antibiotic on subsidence of the lesions.

Gewin and Friou[63] described a patient with endocarditis due to *Staphylococcus aureus* who received prolonged therapy with chlortetracycline and chloramphenicol and manifested mucosal changes in the mouth and gastrointestinal tract, skin lesions and peripheral neuritis. The findings suggested deficiency of several components of the vitamin B complex and a complicating fungous infection of the skin. Visual disturbances and retinal changes compatible with mild optic neuritis were noted. The liver was

enlarged, and there was bleeding from the gastrointestinal tract. The blood level of prothrombin was lowered but not to a degree sufficient to account for the hemorrhage. Moderate doses of vitamins were only partially effective in curing the signs attributed to vitamin deficiency until antibiotics were discontinued. The authors suggested that the mechanism of these effects might be either destruction of intestinal bacteria essential to synthesis or utilization of the components of the vitamin B complex, or a competitive blockage of intracellular metabolism by the antibiotics. If the latter view should prove correct, parenteral therapy with potent vitamins might lessen the effectiveness of antibiotics. In this regard it is of interest that Foster and Pittillo[64] found that riboflavin reversed the inhibition of growth of *Escherichia coli* induced by chlortetracycline and that the relation was competitive. The effective inhibitory level of chlortetracycline varied inversely with the riboflavin content of the cell. The suggestion was made that dietary control might be a valuable adjunct to antibiotic therapy.

Rege and Sreenivason[65] reported that chlortetracycline inhibited the synthesis of pentose nucleic acid and desoxypentose nucleic acid by *Lactobacillus casei* and that folic acid, or high concentrations of vitamin B_{12}, offered protection against this inhibition. Inhibition of normal nucleic acid metabolism of micro-organisms has been noted for penicillin. In addition, cultural conditions favoring the pentose nucleic acid content of bacterial cells enhanced resistance of *Haemophilus pertussis* to chlortetracycline. Di Raimondo, Orabona and Albano[66] studied interference between components of the vitamin B complex and penicillin in experimental staphylococcal infection in mice. The mortality was 52 per cent in control mice receiving no penicillin, 0 in mice receiving penicillin alone and 37.5 to 55 per cent in mice receiving penicillin and pyridoxine, nicotinic acid, folic acid or vitamin B_{12} parenterally three hours before intraperitoneal injection of *Staph. aureus*. Other components of the vitamin B complex had no, or slight, action.

The preceding findings suggest that administration of certain antibiotics may lead to deficiency of some of the vitamins essential to human nutrition. The mechanism of this action remains uncertain; the effect may be due to an influence on the intestinal flora, to competitive blocking of intracellular metabolism or to anorexia, vomiting and diarrhea, which often accompany antibiotic administration. The validity of the mucous-membrane and skin changes as signs of vitamin deficiency may be questioned since similar lesions occur in fungous infections, which may develop during antibiotic therapy.

Efficacy of Antibiotic and Vitamin Combinations

There have been few reports of the use of vitamins in combination with antibiotics in the treatment of infections. Prigot and Maynard[67] treated 35 patients with surgical infections with such combinations and reported that therapy was tolerated well; all patients recovered, and there were no toxic or allergic reactions. No control group was studied. Milberg and Michael[68] administered tetracycline with water-soluble vitamins to 45 patients with acute illness and found no change in the effectiveness of therapy when compared with previous studies in which tetracycline was used alone. There was no evidence of better therapeutic response or improved clinical status with combined therapy. Side reactions were relatively infrequent; gastrointestinal disturbances occurred in 4 of 53 subjects who received vitamins and tetracycline and in 2 of 10 patients given oxytetracycline with vitamins. Loughlin and Mullin[69] reported the use of tetracycline and oxytetracycline in combination with vitamins in the treatment of amebiasis, yaws, pinta and tropical ulcer, in Haiti. These infections were often associated with undernutrition and deficiency states. The authors presented no data but stated that ulcerous lesions of late yaws, ulcers of amebiasis in the large intestine and tropical ulcer appeared to heal more rapidly with vitamin and antibiotic combinations than with antibiotics alone. The vitamins had no patent inhibitory effects on the antiparasitic activity of the antibiotics, and there was an absence of notable toxic reactions. Planson[70] reported that administration of components of the vitamin B complex to 45 subjects prevented mucocutaneous reactions during therapy with chloramphenicol and chlortetracycline whereas 31 such reactions developed in 102 subjects receiving antibiotics alone.

The paucity of information on the efficacy of antibiotic and vitamin combinations precludes any attempt to evaluate this method of therapy at present. There is a real need for carefully controlled experiments in a significant number of comparable subjects who have similar infections.

Summary and Conclusions

The influence of vitamin nutrition on resistance to specific infections in the human subject remains largely unknown. There is considerable evidence that infections, and other stress situations, influence the requirement or utilization of certain vitamins, but there are few, if any, data regarding exact requirements in specific pathologic states. The therapeutic value of administration of large doses of vitamins in infections has not been appraised critically.

Antibiotic administration has been found to have a sparing action on the requirement of certain vitamins in several animal species. This action appears to be an effect on the intestinal flora and is not observed when the diet is adequate in the vitamins in question. A few studies suggest that under certain circumstances antibiotics may spare the requirement of some of the vitamins in man. There is also evidence that under other conditions administration of antibiotics may lead to vitamin deficiency in human sub-

jects. Some of the lesions developing in the course of antibiotic therapy that have been attributed to an inadequate supply of vitamins may be explained by complicating fungous infections, but other lesions may reflect a true deficiency state.

The possibility that antibiotics induce vitamin deficiency by competitive blockage of intracellular metabolism has not been ruled out. If this should be true, administration of vitamins might lessen the effectiveness of antibiotics.

The efficacy of administration of antibiotic and vitamin combinations, as compared with antibiotics alone, in the therapy of specific infections has not been tested in controlled experiments. Until more information is available, it is impossible to state which vitamins, if any, should be administered with which antibiotic in the treatment of a given infection.

The importance of maintaining adequate nutrition during the course of infections, and many other diseases, has been recognized increasingly in recent years, but much remains to be learned about what constitutes adequate nutrition. Calories, water, protein, vitamins and minerals must all be supplied in proper amounts, and each patient presents an individual problem. There is no magic formula that can relieve the practicing clinician of detailed analysis of all facets of the patient's nutritive state.

The many unknowns in relation between nutrition and infection and nutrition and antibiotics should be a challenge to scientists working in these fields. A concerted attack should lead to solution of many current problems.

References

1. Pollack, H., and Halpern, S. L. *Therapeutic Nutrition*. Washington, D. C.: National Academy of Sciences and National Research Council, 1952. Publication 234.
2. National Academy of Sciences and National Research Council — Food and Nutrition Board. Statement on need for critical reconsideration of Publication 234. *Therapeutic Nutrition*, April, 1955.
3. Clark, P. F., McClung, L. F., Pinkerton, H., Price, W. H., and Schneider, H. A. Influence of nutrition in experimental infection. *Bact. Rev.* **13**:99-134, 1949.
4. Schneider, H. A. Recapitulation and prospects. *Ann. New York Acad. Sc.* **63**:314-317, 1955.
5. *Idem*. Nutrition and resistance to infection: strategic situation. *Vitamins & Hormones* **4**:35-70, 1946.
6. Robertson, E. C., and Tisdall, F. F. Nutrition and resistance to disease. *Canad. M. A. J.* **40**:282-284, 1939.
7. Getz, H. R., Long, E. R., and Henderson, H. J. Study of relation of nutrition to development of tuberculosis: influence of ascorbic acid vitamin A. *Am. Rev. Tuberc.* **64**:381-393, 1951.
8. Suzman, M. M. Discussion of Kinsell.[21]
9. Frye, W. W. Nutrition and intestinal parasitism. *Ann. New York Acad. Sc.* **63**:175-185, 1955.
10. Terzian, L. A., Stahler, N., and Miller, H. Study of relation of antibiotics, vitamins and hormones to immunity to infection. *J. Immunol.* **70**:115-123, 1953.
11. Hill, C. H., and Garren, H. W. Effect of high levels of vitamins on resistance of chicks to fowl typhoid. *Ann. New York Acad. Sc.* **63**:186-194, 1955.
12. Wooley, J. G., and Sebrell, W. H. Nutritional deficiency and infection. I. Influence of riboflavin or thiamine deficiency on fatal experimental pneumococcal infection in white mice. *Pub. Health Rep.* **57**:149-161, 1942.
13. Axelrod, A. E., and Pruzansky, J. Role of vitamins in antibody production. *Ann. New York Acad. Sc.* **63**:202-213, 1955.
14. Holt, L. E., Jr. Thiamine requirement of man. *Federation Proc.* **3**:171-178, 1944.
15. National Academy of Science and National Research Council — Food and Nutrition Board. *Recommended Dietary Allowances*. (Publication 302.) Washington, D. C.: Government Printing Office, 1953.
16. Goldsmith, G. A. Unpublished data.
17. *Idem*. Nutrition principles in treatment. In Smith, A., and Wermer, P. L. *Modern Treatment*. 1146 pp. New York: Hoeber, 1953. Pp. 642-688.
18. Kagan, B. M. Observations on infection and certain vitamins. *Ann. New York Acad. Sc.* **63**:214-219, 1955.
19. Ershoff, B. H. Conditioning factors in nutritional disease. *Physiol. Rev.* **28**:107-137, 1948.
20. Pollack, H., and Bookman, J. J. Riboflavin excretion as function of protein metabolism in normal, catabolic and diabetic human being. *J. Lab. & Clin. Med.* **38**:561-573, 1951.
21. Kinsell, L. W. Nutritional and metabolic aspects of infection. *Ann. New York Acad. Sc.* **63**:240-251, 1955.
22. Ershoff, B. H. Nutrition and anterior pituitary with special reference to general adaptation syndrome. *Vitamins & Hormones* **10**: 79-140, 1952.
23. *Idem*. Nutrition and stress. *Nutrition Rev.* **13**:33-36, 1955.
24. Govier, W. M. Rationale for use of vitamins in therapy of shock and anoxia. *J.A.M.A.* **126**:749, 1944.
25. Andreae, W. A., and Browne, J. S. L. Ascorbic acid metabolism after trauma in man. *Canad. M. A. J.* **55**:425-432, 1946.
26. Levenson, S. M., et al. Ascorbic acid, riboflavin, thiamin, and nicotinic acid in relation to severe injury, hemorrhage, and infection in human. *Ann. Surg.* **124**:840-856, 1946.
27. Kühnau, J. Fluid balance during infection with reference to protein and mineral enzyme systems. *Ann. New York Acad. Sc.* **63**: 220-229, 1955.
28. Elvehjem, C. A. Role of intestinal bacteria in nutrition. *J. Am. Dietet. A.* **22**:959-963, 1946.
29. Najjar, V. A., and Barrett, R. Synthesis of B vitamins by intestinal bacteria. *Vitamins & Hormones* **3**:23-48, 1945.
30. Jukes, T. H., and Williams, W. L. Nutritional effects of antibiotics. *Pharmacol. Rev.* **5**:381-420, 1953.
31. Mickelson, O. Nutritional aspects of antibiotics. *J. Am. Dietet. A.* **29**:221-229, 1953.
32. Stokstad, E. L. R. Antibiotics in animal nutrition. *Physiol. Rev.* **34**:25-51, 1954.
33. Linkswiler, H., Baumann, C. A., and Snell, E. E. Effect of aureomycin on response of rats to various forms of vitamin B_6. *J. Nutrition* **43**:563-573, 1951.
34. Ilft, F. S., and Schwarz, K. Prevention of certain B vitamin deficiencies with ascorbic acid or antibiotics. *Federation Proc.* **11**: 200, 1952.
35. Lih, H., and Baumann, C. A. Effects of certain antibiotics on growth of rats fed diets limiting in thiamin, riboflavin or pantothenic acid. *J. Nutrition* **45**:143-152, 1951.
36. Schendel, H. E., and Johnson, B. C. Studies of antibiotics in weanling rats administered suboptimal levels of certain B vitamins orally and parenterally. *J. Nutrition* **54**:461-468, 1954.
37. Guggenheim, K., Halevy, S., Hartman, I., and Zamir, R. Effect of antibiotics on metabolism of certain B vitamins. *J. Nutrition* **50**:245-253, 1953.
38. Halevy, S., Diamant, E. J., and Guggenheim, K. Effect of antibiotics on metabolism of nicotinic acid, biotin and folic acid in rats. *Brit. J. Nutrition* **9**:57-62, 1955.
39. Fidanza, A., Guinchi, G., Rutigliano, M. L., Scuro, L. A., and Sarici, F. Effect of chloramphenicol on growth of rats fed with diet deprived of pantothenic acid. *Boll. Soc. ital. biol. sper.* **28**: 1903, 1952.
40. Calet, C., Rerat, A., and Jacquot, R. Action d'épargne des antibiotiques pour quelques vitamines du groupe B. *Compt. rend. Acad. Sc.* **236**:2340-2342, 1953.
41. Sauberlich, H. E. Effect of aureomycin and penicillin upon vitamin requirements of rat. *J. Nutrition* **48**:99-108, 1952.
42. Cravioto-Munoz, J., Poncher, H. G., and Waisman, H. A. Vitamin B_{12} sparing action of aureomycin in rat. *Proc. Soc. Exper. Biol. & Med.* **77**:18, 1951.
43. Di Raimondo, F., Angarano, D., Mannino, N., and Trinchese, L. Effetti collaterali di antibiotici nel ratto, con particolare riguardo al metabolismo di vitamine del complesso B. *Internat. Ztschr. f. Vitaminforsch.* **24**:276-294, 1952.
44. Di Raimondo, Mannino, N., and Trinchese, L. Effetti collaterali di antibiotici nel ratto: contenuto del fagato in vitamine del complesso B e quadro istologico dopo prolungato trattamento. *Internat. Ztschr. f. Vitaminforsch.* **24**:294-301, 1952.
45. Biely, J., and March, B. Effect of aureomycin and vitamins on growth rate of chicks. *Science* **114**:330, 1951.
46. Coates, M. E., Harrison, G. D., Harrison, G. F., and Kon, S. K. Effect of antibiotics on growth of chicks deprived of vitamins of B complex. In Proceedings of the Biochemical Society. *Biochem. J.* **49**:68, 1951.
47. Ahmquist, H. J., and Maurer, S. Effect of antibiotic, antioxidant, and fat on conversion of carotene to vitamin A in chicken. *Arch. Biochem.* **55**:297, 1955.
48. Gabuzda, G. J., Jackson, G., and Grigsby, M. E. Effect of aureomycin upon nitrogen balance and urinary riboflavin excretion in undernourished men. *J. Clin. Investigation* **31**:631, 1952.
49. Gabuzda, G. J., Gocke, T. M., and Love, B. D. Metabolic effects of antibiotics administered to undernourished men. *J. Clin. Investigation* **32**:570, 1953.
50. Davis, R. L., and Chow, B. F. Content of radioactive vitamin B_{12} in feces of rats fed Co^{60} and aureomycin. *Proc. Soc. Exper. Biol. & Med.* **77**:218-221, 1951.
51. Haubold, H., Loew, W., and Kolb, E. Einwirkung von Penicillin auf den Vitamin A-Gehalt des Serums sowie auf die Nachtsichtigkeit. *München med. Wchschr.* **95**:792-796, 1953.
52. Michon, P., de Lavergne, E., Picard, J. M., Schmidt, J., and Burdin, J. C. A propos d'une eventuelle carence en vitamine K sous l'influence des antibiotique à action intestinale. *Semaine d. hôp. de Paris* **30**:1800-1802, 1954.
53. Di Raimondo, F., Angarano, D., Mannino, N., and Trinchese, L. Effetti collaterali di alcuni antibiotici, in soggetti sani e in malati, con particolare riguardo all' eliminazione urinaria di vitamine del complesso B. *Internat. Ztschr. f. Vitaminforsch.* **24**:302-317, 1952.
54. Sauberlich, P. Effect of oral administration of streptomycin on urinary excretion of B vitamins in man. *J. Nutrition* **47**:275-287, 1952.
55. Scuro, L. A. Studio dell' eliminazione urinaria di acido pantotenico in corso di trattamente antibiotico. *Acta vitamin.* **7**:143-146, 1953.
56. Smith, D. T. Disturbance of normal bacterial ecology by administration of antibiotics with development of new clinical syndromes. *Ann. Int. Med.* **37**:1135-1143, 1952.
57. *Fungus Infections Complicating Antibiotic Therapy: Excerpts and abstracts of the published literature*. New York: E. R. Squibb & Sons, 1955.

58. Downing, J. G. Black tongue as result of antibiotic therapy: report of case. *New Eng. J. Med.* **242**:1013, 1950.
59. Krakoff, I. H., Karnofsky, D. A., and Burchenal, J. H. Effects of large doses of chloramphenicol on human subjects. *New Eng. J. Med.* **253**:7-10, 1955.
60. Schulte, W. C. B complex avitaminosis with oral aureomycin. *Oral Surg.* **5**:279, 1952.
61. Harris, H. J. Aureomycin and chloramphenicol in brucellosis: with special reference to side effects. *J.A.M.A.* **142**:161-165, 1950.
62. Ellinger, P., and Shattock, F. M. Nicotinamide deficiency after oral administration of penicillin. *Brit. M. J.* **2**:611-613, 1946.
63. Gewin, H. M., and Friou, G. J. Manifestations of vitamin deficiency during aureomycin and chloramphenicol therapy of endocarditis due to staphylococcus aureus: report of case. *Yale J. Biol. & Med.* **23**:332-338, 1951.
64. Foster, J. W., and Pittillo, R. F. Metabolite reverse of antibiotic inhibition, especially reversal of aureomycin inhibition by riboflavin. *J. Bact.* **66**:478-486, 1953.
65. Rege, D. V., and Sreenivason, A. Influence of folic acid and vitamin B_{12} on impairment of nucleic acid synthesis in lactobacillus casei by aureomycin. *Nature* (London) **173**:728, 1954.
66. Di Raimondo, F., Orabona, M. L., and Albano, O. Nutrizione e terapia antibiotica: ulteriori ricerche sulle interferenze tra vitamine del complesso B e penicillina nella infezione stafilococcica sperimentale. *Boll. Ist. sieroterap. Milan* **32**:118-123, 1953.
67. Prigot, A., and Maynard, A. de L. Fortified broad spectrum antibiotics as adjuncts in treatment of surgical infections of young, aged, and debilitated patient. *Ann. New York Acad. Sc.* **63**: 230-239, 1955.
68. Milberg, M. B., and Michael, M., Jr. Antibiotics and nutrition in infections. *Ann. New York Acad. Sc.* **63**:252-257, 1955.
69. Loughlin, E. H., and Mullin, W. G. Certain aspects of deficiency diseases of tropics and treatment of some related infections. *Ann. New York Acad. Sc.* **63**:276-300, 1955.
70. Planson, E. Prophylaxie des accidents cutanéo-muqueux dus à la chloromycétine et à l'auréomycine par le complexe B. *Presse méd.* **59**:673, 1951.

MEDICAL INTELLIGENCE

A DEVICE FOR RAPIDLY DERIVING THE HEMATOCRIT OF BLOOD CENTRIFUGED IN UNGRADUATED TUBES

ALAN RICHARDSON JONES, M.B., B.S. (Lond.)*

BOSTON

IN a previous communication[1] mention was made of a device for rapidly and accurately reading the relative length of the packed red-cell column in the ungraduated capillary tubes used in the Guest and Siler[2] microhematocrit technic. The purpose of this communication is to describe this device in greater detail.

The usual methods for measuring hematocrit levels in ungraduated capillary tubes consist either of laying the tube on a ruler and converting the measured lengths of the plasma and packed cell columns to hematocrit percentage by simple computation or of placing the tube against a specially prepared scale of divergent lines. The former method is both inaccurate and tedious, but its accuracy may be improved if a traveling microscope is substituted for the ruler. The latter method is rapid but requires a high level of manual dexterity to position the tube critically on the scale, and this has been found in practice to lead to fatigue-induced error if more than a dozen tubes are measured in quick succession.

The device described here enables high accuracy of reading to be achieved, together with ease and rapidity of operation.

PRINCIPLE OF OPERATION

The instrument is essentially a circular slide rule. Linear dimensions (such as the length of the total blood column or of the packed cell column) of blood in a capillary tube are converted to logarithmic dimensions on a scale. Suitable choice of a reference point on the logarithmic scale will then permit all linear dimensions referred to it to be expressed automatically as ratios.

CONSTRUCTION

The instrument† consists of four parts.

Base

This is a cast-iron circular base supporting a shaft upon which the other components are mounted.

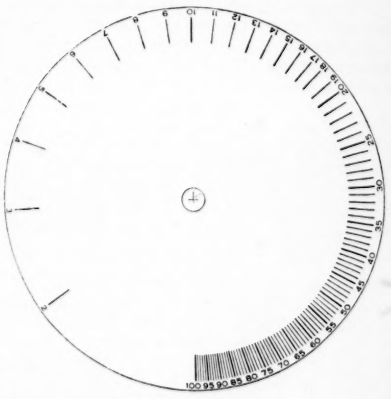

FIGURE 1. *Logarithmic Scale.*

Logarithmic Scale

This is a disk, 19.0 cm. in diameter, made of rigid material such as sheet metal or 0.16-cm. Lucite sheet. Around its periphery is drawn a logarithmic scale reading from 1 to 100 so that the range of 99 divisions occupies the whole circumference (Fig. 1). This disk is mounted centrally on the main shaft and is free to turn on it with a minimum of play or shake.

*Research associate, Department of Pediatrics, Harvard Medical School; associate director, Blood Grouping Laboratory of Boston; research associate in hematology, Children's Medical Center.

†Available from International Equipment Company, Boston.

Logarithmic Spiral

This is a second disk, 17.5 cm. in diameter, made of material similar to that of the scale. A circle of 2.5-cm. diameter is inscribed about its center. With this circle as a starting point, a logarithmic spiral is drawn on the disk, any radius being inscribed on the disk to constitute a reference line, and, between the inner circle and periphery of the disk, this radius is divided into 100 equal parts. The disk is laid on a common center with the logarithmic scale, and the drawn radius is set opposite the "100" division on the scale. The intersection of the radius with the scale thus gives the starting and finishing points for a spiral line to be drawn on the disk, and it is now a simple matter to prick out the main points of such a curve by the use of the equal intervals marked on the radius and the divisions of the logarithmic scale that numerically correspond to them as co-ordinates. The finished curve has the appearance shown in Figure 2. The disk is placed on the shaft above the scale, from which it is separated by a spring washer.

Tube Holder

The capillary tube containing the centrifuged blood is placed in a groove in a Lucite arm (Fig. 3). The

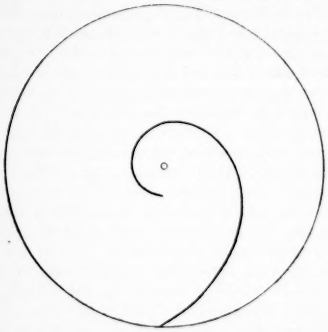

FIGURE 2. *Logarithmic Spiral.*

arm is firmly fixed at one end to the shaft, and the other end projects over the logarithmic scale. The underside of the arm carries a line engraved at its outer end to represent the continuation of the groove; this is the cursor. At the central end of the groove and at right angles to it there is a reference line that is tangential to the inner circle on the logarithmic spiral disk.

OPERATION

The capillary tube containing centrifuged blood is placed in the groove in the arm of the instrument with the sealed end toward the central shaft. The position of the tube is adjusted so that the bottom of the packed cells coincides with the reference line on the arm. The logarithmic spiral and the logarithmic scale are now rotated independently so that the logarithmic spiral just cuts the air-plasma interface, and the "100" graduation of the logarithmic scale is brought into coincidence with the cursor line.

Both disks are now rotated, maintaining the same relative position to one another, until the spiral line

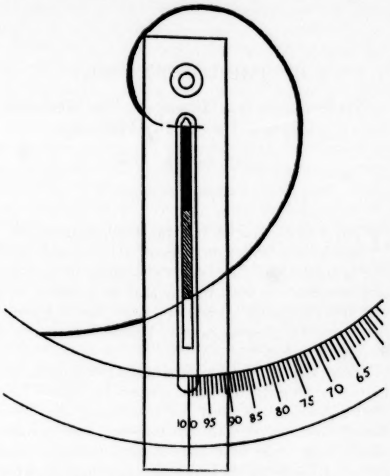

FIGURE 3. *Tube Holder, Showing a Capillary Hematocrit Tube in Place and Indicating the Relative Position of the Two Disks at the "100 per Cent" Setting.*

cuts the plasma-cell interface. At this moment the graduation on the logarithmic scale that lies under the cursor line represents the packed cell volume expressed as a percentage of the total volume of the specimen.

DISCUSSION

This instrument has been used extensively in the Hematologic Unit of the Children's Medical Center in Boston, with excellent results. It requires little skill in operation and yields results that appear to be free from fatigue-induced error. The precision of the device is a function of the accuracy with which the scale and curve are drawn. No difficulty is experienced in defining the moment of intersection of the blood interfaces with the curve. Trials of actual observations made by four independent operators give results that agree within five tenths of a scale division. This is at least as good as the accuracy obtained in reading the conventional graduated Wintrobe hematocrit tube and is considerably better than may be

achieved by the use of a divergent line or "perspective" graph.

I am indebted to the International Equipment Company, Boston, for help and encouragement in developing this instrument.

References

1. McGovern, J. J., Jones, A. R., and Steinberg, A. G. Hematocrit of capillary blood. *New Eng. J. Med.* **253**:308-312, 1955.
2. Guest, G. M., and Siler, V. E. Centrifuge method for determination of volume of cells in blood. *J. Lab. & Clin. Med.* **19**:757-768, 1934.

BY THE LONDON POST

No Reprieve for Heroin — The Medicine Cupboard — Family Planning

JOHN LISTER, M.D.

LONDON, ENGLAND

THE much debated ban on the manufacture of heroin took effect on January 1. In recent weeks the proposed ban has been the subject of considerable discussion in both the lay and the medical press, and the *Times* has given the matter unusual prominence in the correspondence columns and also in leading articles.

There has never been the slightest dispute that heroin is possibly the most dangerous drug of addiction known, nor that the concern of the World Health Organization is anything but fully justified. Furthermore, the standing medical advisory committee of the Central Health Services Council, which advises the Minister of Health, is composed of medical men and women of the highest professional standing and of widely differing experience, and when they stated their view that heroin is not indispensable it is not altogether surprising that the Minister accepted this view as probably being representative of the medical profession. On the other hand the validity of the advice of the advisory committee has since been disputed, and it has been claimed that many of the members of this committee hold appointments divorced from the trials of practice.

Since the announcement of a definite decision to ban the manufacture of heroin there have been many protests. These have come chiefly from the British Medical Association, which was not officially consulted, and from the Fellowship for Freedom in Medicine, whose members maintain that the banning of a drug that some physicians may wish to use is an infringement of the freedom of medical practice.

Those who have written letters to the newspapers (and they include not only medical men but also patients who have had experience with the drug) have shown that there are many who believe that heroin is a more efficient pain-relieving and cough-depressing drug than any other available. They have also expressed doubts whether the banning of the manufacture of heroin will necessarily reduce the prevalence of addiction to the drug. In this respect, Sir Cecil Wakeley said that the experience of the United States ought to be considered. He quoted the recent statement of Dr. Herbert Berger at the International Conference of Criminology, who is reported as saying that it would be a fatal error if Great Britain followed the example of the United States, where there is a strong move in both medical and political circles to have the ban lifted.

Other writers have told how many hospitals have ordered large stocks of heroin so that they will have adequate supplies available — at any rate for a considerable time. Finally, many correspondents have called upon the Government to postpone the ban so that the matter might be referred to a representative committee in order that a more authoritative medical view might be obtained.

In spite of all the publicity that has been given to the matter, and in spite of all the representation made, the Government has reaffirmed its decision to impose the ban. Sir Russell Brain and four colleagues who serve on the standing medical advisory committee have said that the committee, believing adequate substitutes to exist, took the view that the importance of co-operating with almost all the other countries in the world in the fight against heroin addiction outweighed the desirability of allowing doctors to prescribe the drug if they wished. They understood and respected the opposite view and said that the decision involved a choice of social values that cannot be made by doctors alone, but only by the Government. There is no doubt that the choice has been one of social values, and in spite of the divergence of medical opinion in this country, the Government has decided to stand by what it considers to be its obligation as a member of a world community rather than by what might be regarded as a domestic social responsibility.

For the time being, this decision will no doubt close this controversial matter, but not without considerable misgiving on the part of the many people who believe that a grave choice in social values has possibly been wrongly made.

* * *

"Purges, nerve sedatives, tonics, rejuvenators, smell banishers and night drinks" — these are the patent medicines to which Dr. Mackenzie Wintle, medical officer for South Oxfordshire, believes that the public is becoming increasingly addicted. He thinks that nearly all could be "thrown into the river" with no loss to those who take them and suggests that "palatable purgatives" should be the first to go.

A visit to the medicine cupboard of any house with such remarks in mind would surely be revealing. On close examination it might well be decided that the cupboard had become a museum rather than

a first-aid post. It is rare for a medicine to be quite finished, and among the lint and the bandages the past would come to light. Half-empty pots of ointment, half-used bottles of linctus and boxes containing brightly colored pills prescribed for some visiting relative of long ago would all be there. More careful scrutiny would probably disclose a variety of powders for dyspepsia, tonics for the nerves and sundry cures for colds.

The gullibility of the public toward publicly advertised medicine has always been criticized by the medical profession; the tax collector seized his opportunity and first imposed a tax on quack remedies as long ago as 1783. At the present time, the cure for hypochondria is more firmly in the doctor's hands than before because only drugs of proved value may be prescribed on National Health Service prescriptions. In spite of this, the practitioner is frequently criticized for overprescribing. This is only natural when the cost is being borne by the public, but much criticism of new drugs is misdirected. The introduction of new preparations often represents medical advance achieved by costly research that has to be paid for. On the other hand, the craving for medicine is still on the increase, and this should surely be resisted in all cases in which the remedy is of no therapeutic value. The release of cortisone and hydrocortisone to general practitioners has only just taken place, and because family doctors have little experience with these preparations, the Ministry of Health has warned all practitioners to exercise the greatest care in their use. It is to be hoped that they will be able to resist the demands of their drug-conscious patients, who may well claim that their craving for medicine is yet another phenomenon of stress.

* * *

Twenty-five years ago the Family Planning Association was founded to co-ordinate the work of five existing organizations. The late Lord Horder was the first president and still held office at the time of his death, and under his guidance the small groups that originally combined were built up into a welfare service that has grown beyond recognition. Apart from giving advice on contraception the Association has given much help to the infertile marriage.

During the recent Silver Jubilee celebrations the Minister of Health made an official visit to one of the Association's clinics. He remarked that the position held by the Association today could not have been conceived of by the pioneers of the movement twenty-five years ago. He was happy that much of the prejudice and ignorance had been swept away and that its work is now accepted as part of the ordinary affairs of life. In congratulating the Association on bringing happiness to many families Mr. MacLeod added that there are many thousands of people in this country whose different views on family planning should be respected. Although greatly stressing voluntary and responsible parenthood one great Christian church and many individual Christians of other persuasions have deep convictions of their own about what methods of family planning are consistent with their faith. They reject the view of the majority that contraception is morally harmless. Because of this division of opinion a free community must accept and leave room for both views, and it is desirable that the family-planning centers remain a voluntary movement and thus free of control or direction by the State.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42041

PRESENTATION OF CASE

A nineteen-year-old college student was admitted to the hospital because of abdominal pain.

Two weeks previously he noted mild epigastric pain and anorexia. Three days later he was afebrile,

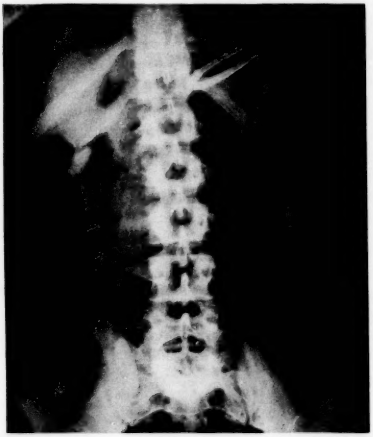

FIGURE 1. *Anteroposterior Film of the Abdomen, Showing a Laminated Calculus Overshadowing the Proximal Ascending Colon.*

without localizing signs or symptoms. Tincture of belladonna and Amphojel were given, with relief of symptoms. He remained well until the day before entry, when the epigastric pain associated with nausea recurred. The pain, which was steady with occasional exacerbations relieved by the vomiting of bile-stained fluid, was generalized over the abdomen but worse in the epigastrium. It became progressively worse and was associated with severe bilateral testicular pain. On the day of admission he passed a normal-appearing stool.

Physical examination showed a well nourished boy writhing with severe abdominal and testicular pain as well as bilateral shoulder pain. The abdomen was

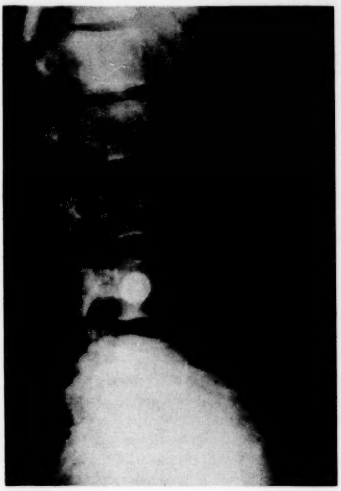

FIGURE 2. *Lateral Film of the Abdomen. The calcification is noted to lie posterior to the colon.*

soft and nontender except for tenderness in the right lower quadrant, which was not a constant finding. There was no rebound tenderness. Peristalsis was present and normal. Rectal examination was negative.

The temperature was 99.8°F. by rectum, the pulse 72, and the respirations 20. The blood pressure was 120 systolic, 80 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 15.1 gm. per 100 ml. and a white-cell count of 13,000. The prothrombin time was 14.5 seconds (normal, 13 seconds). X-ray films of the abdomen demonstrated a 17-mm. laminated calculus lying in the right lower quadrant posteriorly in the region of the cecum. The bowel contained considerable gas and fecal material (Fig. 1 and 2).

An operation was performed one hour after admission.

DIFFERENTIAL DIAGNOSIS

DR. WILLIAM C. QUINBY, JR.*: The short protocol describes the illness of a nineteen-year-old boy, an illness so acute that it led to operation an hour after admission. After a bout of epigastric pain and anorexia, which probably lasted three days (because of

*Assistant in surgery, Massachusetts General Hospital.

the note of an examination and the relief from belladonna and Amphojel), he was well for ten days. Then the acute illness began with what I interpret as rapidly progressing symptoms, both in intensity and in extent of the anatomic regions affected directly or indirectly.

The pain fits no classic diagnostic pattern. Its onset was not clearly described. It was first epigastric and then generalized and constant. Exacerbations were relieved by the vomiting of bile-stained fluid, but the pain remained most severe in the epigastrium. It was accompanied by severe testicular pain and ultimately by bilateral shoulder pain. This strong youth writhed in pain; yet he showed only inconstant right-lower-quadrant tenderness and no generalized abdominal tenderness, spasm or rebound tenderness. Peristalsis and stools that day were normal, and rectal examination was negative. The flanks, the costovertebral angles and the testes were not mentioned in the protocol. The "vital signs" were normal. The only abnormal laboratory finding was the white-cell count of 13,000; a differential count was not reported. But the abdominal x-ray film showed something startling, which may or may not contribute to the specific diagnosis. I shall have to lean heavily on Dr. Hanelin for help.

Dr. Joseph Hanelin: Anteroposterior and lateral views of the abdomen, which were taken within the hour before the operation, clearly show a laminated calcification, approximately 2 cm. in diameter, lying in the right side of the abdomen posterior to the proximal ascending colon (Fig. 1 and 2). It may even impinge upon and cause extrinsic pressure along the posterior wall of the colon. I can see no other calculus. The distribution of the gas in the ascending colon is interesting; there are multiple small bubbles, which are probably in the lumen of the bowel but may be abnormal air collections. If the latter is true, one wonders about pneumatosis cystoides. There is a tube that is coiled in the stomach.

Dr. Quinby: Can you see the right kidney?

Dr. Hanelin: I can outline it partially; it is not obviously abnormal. The left psoas shadow is quite clearly seen; the right is partially obscured by gas in the abdomen.

Dr. Quinby: Is there air in the biliary tree?

Dr. Hanelin: There is no air that I can detect in the liver.

Dr. Quinby: You think this is an extraluminal calculus, then?

Dr. Hanelin: I think it is retrocolic — probably outside the bowel wall.

Dr. Quinby: A calcified mesenteric lymph node would not look like this, would it?

Dr. Hanelin: It would be rare indeed for us to see a laminated calcification of this type in a lymph node.

Dr. Quinby: Assuming a normally placed right kidney, a normally placed right ureter would run medial to the calcification, would it not?

Dr. Hanelin: Yes; it would.

Dr. Quinby: Is there any evidence of intestinal obstruction in the small bowel itself?

Dr. Hanelin: No.

Dr. Quinby: The interpretation of the gas shadows in the region of the ascending colon is difficult. You are suspicious that the gas may be in the wall of the bowel; could it be retroperitoneal?

Dr. Hanelin: I do not think so; a good bit of it lies anteriorly.

Dr. Robert E. Scully: I might add a few points about the physical examination from the record. There was no definite testicular tenderness. The patient was moving about so much because of the pain that he could not be examined until he had been given Demerol.

Dr. Quinby: The chief question is whether the calculus seen in the x-ray film is the key to the problem or is a totally unrelated finding. I shall assume that the former point is true. Urinary-tract calculi can be laminated and can attain this size. Usually, however, they are not in this position. I cannot place the stone within the kidney pelvis since the evidence indicates that the kidney was in normal position. It appears to lie too far laterally for me to believe that it was in the ureter. The history is quite compatible with the passage of a renal stone, however. Reference of pain to the epigastrium and to various parts of the abdomen is well recognized as a pitfall in the diagnosis of urinary-tract disease. The urinalysis need not necessarily be strikingly abnormal if the stone has created a complete block of the urinary tract. The radiation of the pain to the testis is characteristic of colic of the lower end of the ureter, for there is an anatomically associated nerve supply to both areas. Bilateral radiation is not significant in itself, although with a stone in one ureter, the colic and radiation of pain are usually unilateral. I should be surprised, however, if a careful examination of the flanks and costovertebral angles would not lead one to suspect this diagnosis even though the patient was writhing in pain. The absence of local physical findings and the position of the calculus in the x-ray film cause me to eliminate the urinary tract as the site of disease.

One must also consider gallstone ileus, for this patient had a calculus that looked like a gallstone even though it was probably outside the bowel lumen. Although the x-ray film shows no pattern characteristic of ileus or intestinal obstruction, the disease is notorious for the intermittency of obstructive symptoms and for the difficulty of diagnosis. To make this diagnosis I should have to postulate that the stone had passed into the duodenum, either through the biliary tree or through the gall bladder, and that it had increased in size as it descended in the intestine and had produced obstruction. The only ones

that I have ever seen in the x-ray films have cast shadows that are diffuse and difficult to demonstrate. They have looked as though they had an outside layer of inspissated feces. It is said that they are passed as small stones and grow by accretion as they go along. This may explain why bowel obstruction usually occurs low in the ileum, where the bowel is narrow and the stone has become large. The testicular radiation of pain would be unusual, but the other abdominal symptoms might be consistent with gallstone ileus except for the lack of evidence of tenderness over the gall bladder. I shall exclude gallstone ileus on the basis of the patient's age and sex, the absence of a story compatible with cholecystitis and cholelithiasis in the past, the position of the calculus and its clear definition, and the absence of ileus.

In casting about for other sources of calculus that might explain this illness, I have run across a fascinating literature on enteroliths. Enteroliths are found in duodenal or colonic diverticula. In a case reported by Allen and Donaldson[1] an enterolith was found in a Meckel diverticulum. They are variously divided by the authors on the subject into primary enteroliths, which are composed of ingredients available at the site in which the enterolith forms, and secondary enteroliths, which represent additions of inspissated bowel contents to a foreign-body nucleus such as a peach pit or olive stone. I was interested to know that swallowed varnish is a very good nucleus for an enterolith, but I do not think that college students today imbibe much varnish — at least not under that label.

These intestinal stones are curiosities in surgery. They, like a gallstone in the ileum, can produce intermittent intestinal obstruction or local inflammatory processes with abscess or perforation. They often show concentric rings just as this stone did. A whole handful of enteroliths with concentric calcifications have been reported in a patient's megacolon.[2] It is stated that calculi become laminated because alterations in pH and other biochemical factors intermittently favor the precipitation of calcium salts at one time and their solubility at another. The same statement is true for the material that produces the rings that are more radiolucent. In other words the hydrogen-ion concentration and quantity of calcium salts and other material in the intestine vary. Therefore, at one point the stone acquires a layer of calcium salts and at other times a layer of other material, which is often choleic acid. The stones formed in duodenal diverticula are said to be composed almost entirely of choleic acid.[3]

In this particular case, to tie the findings together I should have to place the stone in a retrocecal appendix. I am tempted to do so because enteroliths occur in areas of bowel that are relatively stagnant. The appendix is a blind pouch where a stone can form on whatever nucleus may be present. How does this fit the picture? The patient may have had mild appendicitis as a result of the stone two weeks before admission. This second episode would have to have been an appendicitis rapidly progressing to perforation. The reason I asked Dr. Hanelin about the colonic gas shadows is that sepsis retroperitoneally will produce similar shadows, radiation of pain to the testes and the shoulder, and varied reflex symptoms without much systemic reaction.

If I assume that the stone was unrelated to the illness, it is conceivable that the patient had a duodenal ulcer, the symptoms of which were alleviated somewhat by belladonna and Amphojel two weeks before admission, and that the episode with this violent progression was the result of a leak of intestinal contents retroperitoneally down the right mesenteric root, rather than a free perforation. The epigastrium is almost never soft in a patient who has had symptoms from a perforated ulcer for twenty-four hours, but conceivably it may be. I should expect, however, that the findings would have been definite over the area of migration of the intestinal fluid and that some degree of ileus would have been found.

The general type of abdominal catastrophe that may cause such severe abdominal pain as this is infarction of some organ. Intussusception or a congenital band causing obstruction or volvulus should produce proximal bowel dilatation. I am impressed by the spread of the symptoms and the rapidity with which they spread. The shoulder pain, I gather, was characteristic of diaphragmatic irritation.

DR. GLENN E. BEHRINGER: It was.

DR. QUINBY: It is impossible for me to diagnose a general peritoneal contamination from the facts at hand, and hence I must choose between two diagnoses: an acute retrocecal appendicitis as the result of obstruction to the lumen by an enterolith, with perforation and an abscess retroperitoneally, and perforation of a duodenal ulcer retroperitoneally — which disregards the x-ray finding of stone. I favor the appendicitis.

DR. SCULLY: Dr. Colby, have you a comment?

DR. FLETCHER S. COLBY: The only comment that I have is that a stone in that position could not arise in the urinary tract.

DR. N. JOEL EHRENKRANZ: Has not this type of calcification been described in mesenteric lymph nodes in histoplasmosis?

DR. HANELIN: Rarely, if ever, does this type of calcification occur in lymph nodes. If I am correct in assuming that it lies retroperitoneally, it is not very likely to be in the mesentery.

DR. BENJAMIN CASTLEMAN: Where do you think the stone is, Dr. Hanelin?

DR. HANELIN: I think it could be in a retrocecal appendix or in a mucocele of the appendix. We have seen stones in mucoceles.

DR. SCULLY: Dr. Behringer, would you tell us

your preoperative impression and your operative findings?

DR. BEHRINGER: Several things about this boy were extremely interesting. When I first saw him in the college infirmary he was absolutely manic with pain; he was jumping up, lying on the floor, getting back into bed, curling up, straightening out and rolling over. It was impossible to do more than place a hand on his abdomen and gain the impression that it was not spastic; even an adequate history could not be obtained. I gave him 100 mg. of Demerol intravenously, which made him sleepy but did not affect the pain much. The only patient I have ever seen who demonstrated this much pain had gastric crises associated with tabes. The second interesting point was the radiation of the pain. The testicular pain was excruciating; as he rolled around he held the scrotum with both hands continuously. By the time he was in the operating room he began to complain of bilateral shoulder pain.

CLINICAL DIAGNOSIS

Generalized peritonitis from perforation of appendix or gall bladder.

DR. WILLIAM C. QUINBY, JR.'S, DIAGNOSIS

Retrocecal appendicitis caused by enterolith within appendix, probably with perforation.

ANATOMICAL DIAGNOSIS

Appendicolith, with acute appendicitis.

PATHOLOGICAL DISCUSSION

DR. BEHRINGER: At operation a quick exploration of the right upper quadrant revealed the gall bladder to be soft and easily compressible; there was no evidence of inflammation in the region of the gall bladder. The common duct was of normal size, and there was no evidence of perforation. The appendix, which lay free in the right gutter, was not covered by fibrin and looked remarkably bland on the outside except for a large tumefaction in its center. It looked like the classic picture of the python that had swallowed a pig. Both ends of it were of normal size. The appendix was full of blood and contained a stone.

DR. SCULLY: The stone measured 2 cm. in diameter and had a smooth greenish-black surface. On section it was composed of concentric layers of brittle material around a whitish pultaceous nucleus. The appendix showed mucosal hemorrhage beneath the calculus and areas of intense neutrophilic infiltration in the muscularis. There was no evidence of perforation. When the chemistry laboratory reported that the calculus gave a strongly positive qualitative test for cholesterol, we became intrigued with the possibility that it might have migrated from the gall bladder. However, in a perusal of the literature, which was extensive, but not exhaustive, we were unable to find a single case of gallstone in the appendix reported in sufficient detail to merit authenticity. In several cases stones consisting largely of cholesterol were found.[4] However, here, there was no mention of the presence or absence of associated gall-bladder disease. In 1 case the appendix contained calculi resembling those found in the gall bladder of the same patient, but no chemical analyses were done to prove their identity.[5] With such shaky support from the literature, we requested a quantitative cholesterol level. This proved to be approximately 1 per cent. We also sectioned microscopically the nucleus of the calculus, and found bits of vegetable material. Finally, the patient had a normal Graham test several weeks postoperatively. All these findings, I believe, prove quite conclusively that the calculus was formed in the intestinal tract and not in the gall bladder. The narrowness of the neck of the appendix and the large size of the stone strongly suggest an in-situ origin.

Do you have any other comment, Dr. Behringer?

DR. BEHRINGER: In reconstructing the symptoms I believe that the episode two weeks before entry to the hospital and also most of the symptoms that brought the patient to the hospital were the result, in most part, of spasm of the appendix, especially since the mucosa of the appendix was so traumatized that it was almost completely destroyed and the lumen was full of old blood, both of which must have been caused by appendiceal spasm around the stone.

Applause for Dr. Quinby!

REFERENCES

1. Allen, A. W., and Donaldson, G. A. Meckel's diverticulum containing calculi. *Arch. Surg.* **50**:286, 1945.
2. Harland, D. Multiple calculi in large intestine with review of subject of intestinal calculi. *Brit. J. Surg.* **61**:209, 1954.
3. Grettve, S. Contribution to knowledge of primary true concrements in small bowel. *Acta chir. Scandinav.* **95**:387-410, 1947.
4. Kelly, H. A., and Hurdon, E. *The Vermiform Appendix and Its Diseases.* 827 pp. Philadelphia: Saunders, 1905. Pp. 363 and 364.
5. Bowers, W. F. Appendicitis with especial reference to pathogenesis, bacteriology and healing. *Arch. Surg.* **39**:362-422, 1939.

CASE 42042

PRESENTATION OF CASE

A seventy-two-year-old porter entered the hospital because of abdominal pain.

About seven months previously he began to notice intermittent, sharp nonradiating abdominal pain. Four months later, because of shortness of breath, exertional dyspnea, swelling of the ankles and abdomen, anorexia and weakness, he stopped working. With diuretic and digitalis therapy a month and a half before entry the swelling of the abdomen and ankles decreased. Hospitalization was refused. Because of weakness he remained bed ridden. During the two weeks before admission the abdominal pain, which was relieved temporarily by vomiting and

only slightly by sodium bicarbonate, increased in severity and became localized to the lower abdomen, mostly in the midline. Two days before entry he vomited yellowish-brown undigested food on numerous occasions. There had been no melena, change in bowel habits, hematemesis, jaundice or chest pain. Since the onset of symptoms there had been a 20-pound weight loss. He had consumed several bottles of beer every day and about half a pint of whisky a week.

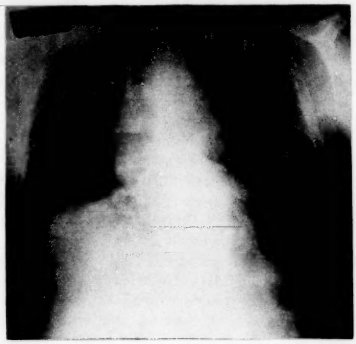

FIGURE 1. *Posteroanterior Film of the Chest, Showing No Appreciable Cardiac Enlargement.*
The diaphragm is elevated, more so on the right, and there is a small amount of fluid in the right pleural space, including the minor septum.

Physical examination showed a small, cachectic, dehydrated, slightly confused, deaf man complaining of abdominal pain. One observer noted slight scleral icterus. The neck veins were flat when he was raised 90° and full and pulsating when he was raised 30°. There was dullness at the right-lung base and a few moist basal rales bilaterally. The leaves of the diaphragm were elevated and moved poorly. The heart was slightly enlarged to the left. There was marked abdominal distention, with diffuse tenderness, especially in the right upper quadrant, and shifting dullness. There was no rebound tenderness. The liver and spleen were not palpated. Bilateral costovertebral-angle pain was noted by one observer. There was + edema of the legs and over the sacrum. No lymphadenopathy was found. There was diminished sensation to pinprick and vibration in the lower extremities. Rectal examination revealed a prostate of twice the normal size, without nodularity or induration.

The temperature was 101.2°F., the pulse 140, and the respirations 24. The blood pressure was 98 systolic, 70 diastolic.

The urine had a specific gravity of 1.015 and gave a + test for albumin; the sediment contained a rare white cell and 0 to 2 hyaline and granular casts per high-power field. Examination of the blood revealed a hemoglobin of 11.8 gm. per 100 ml. and a white-cell count of 5700. The serum nonprotein nitrogen was 42 mg., the fasting blood sugar 102 mg., the uric acid 4.8 mg., the iron 120 microgm., the total protein 5.7 gm., the albumin 3.1 gm., the globulin 2.6 gm., the serum bilirubin 1.5 mg. direct, 3.4 mg. total, the cholesterol 130 mg. and the cholesterol esters 55 mg. per 100 ml. and the alkaline phosphatase 2.7 units. Cephalin flocculation was ++ in forty-eight hours. The prothrombin time was 13.5 seconds (normal, 13 seconds). The serum sodium was 130 milliequiv., the potassium 4.2 milliequiv., the chloride 99 milliequiv., and the carbon dioxide 24 milliequiv. per liter. The serum pH was 7.5. X-ray films of the chest (Fig. 1) showed increased density at the costophrenic angle and thickening of the major fissure on the right. The heart was normal. Abdominal films (Fig. 2) demonstrated a generalized haziness consistent with free fluid in the peritoneal cavity. An electrocardiogram showed a sinus tachycardia of 108. The PR and QRS intervals were 0.14 and 0.08 second respectively. The ST segments were sagging in Leads 1, 2 and aVL; the T waves were low in Leads 2, aVF, V_5 and V_6. Four stool specimens were normal in color and gave negative guaiac tests. Sigmoidoscopic examination was negative.

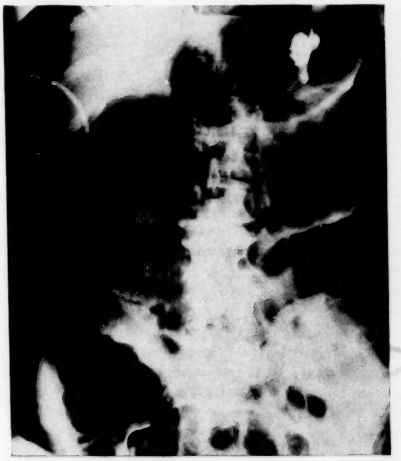

FIGURE 2. *Film of the Abdomen, Showing Dilatation of both Small and Large Bowel.*

On abdominal paracentesis on the first hospital day 1000 ml. of cloudy, greenish-yellow fluid was obtained. The specific gravity was 1.012, and the protein 3.9 gm. per 100 ml.; the fluid contained numerous neutrophils and a few lymphocytes; no

tumor cells were seen; culture showed no growth; smears were negative for acid-fast bacilli, and cytologic examination for malignant cells was negative.

During the first two days in the hospital the patient had episodes of confusion and hallucinations with lucid intervals. Thereafter, he was moribund. With a cardiac regimen and Gantrisin therapy the temperature returned to normal. After the paracentesis there was still considerable abdominal distention, with tenderness in both lower quadrants. No bowel sounds were audible. There was no spasm, guarding or rebound tenderness. No abdominal masses were felt. Gastric aspiration yielded 350 ml. of fluid with much gas. X-ray films demonstrated, in spite of intubation, progressive gaseous distention of the stomach, small intestine and ascending and transverse colon. Barium-enema examination was negative. The patient was catheterized because of small urethral and vesical-neck strictures. In spite of vigorous intravenous therapy there was very little urinary output until the fourth hospital day, when about 600 ml. of urine with a specific gravity of 1.005 was passed.

On the fifth hospital day respirations were noted to be rapid and noisy, with coarse inspiratory and expiratory rhonchi and a few fine rales. The serum nonprotein nitrogen was 82 mg. per 100 ml.; the serum sodium was 124 milliequiv., the potassium 6 milliequiv., the chloride 95 milliequiv., and the carbon dioxide 18 milliequiv. per liter. The serum pH was 7.45. On the sixth hospital day at another abdominal paracentesis, 3245 ml. of cloudy yellow fluid was obtained; the specific gravity was 1.009, and the protein was 2.6 gm. per 100 ml.; the cell count was 6100, with 85 per cent neutrophils, 10 per cent lymphocytes and 5 per cent monocytes; cytologic examination for malignant cells was negative; culture showed no growth. After the paracentesis the liver edge, which was smooth, was felt 2 fingerbreadths below the right costal margin. The spleen was not palpable. No abdominal masses were felt. Two hours later the patient died.

Differential Diagnosis

Dr. Evan Calkins*: It seems to me that the key to this case is the development of ascites. The three most common causes of accumulation of body fluids are diseases of the heart, kidneys and liver. The patient was treated for congestive heart failure and had ankle edema and ascites early. Nevertheless, by the time of admission, despite massive ascites the neck veins were not distended, and the heart was not enlarged. There was only minimal ankle edema. I do not think that heart disease was the cause of the ascites.

Could he have had nephrosis? Again, the distribution of the fluid, being predominantly ascites with very little ankle edema, is against this. Moreover, the urine gave only a + test for albumin, and contained a negligible number of casts and white cells. The total serum protein, albumin and globulin were not altered. I do not believe that there was evidence for nephrosis. Some renal disease was present terminally, but I do not think this was the cause of the ascites.

Laënnec's cirrhosis comes to mind. There was ascites, a history of alcoholism and hepatomegaly at the end of the course, the cholesterol esters were reduced, and the patient was icteric. Nevertheless, there were none of the stigmas of cirrhosis—no spider angiomas, no liver palms, no softening of the testes, no loss of axillary hair and no enlargement of the spleen. Furthermore, the prothrombin time was normal, as was the serum protein concentration and albumin-globulin ratio. For this reason I do not believe that there was sufficient evidence of Laënnec's cirrhosis for it to be the primary cause of the ascites.

Could this have been a primary disease of the peritoneum? Could it have been acute peritonitis? No; the course was too chronic. The patient would not have been walking around for several weeks with swelling of the abdomen as the result of peritonitis. Could it have been chronic tuberculous peritonitis? The persistent ascites, the pain in the lower abdomen, the tenderness hither and yon, the weight loss and the fever are all consistent with tuberculous peritonitis. Nevertheless, I think it would be surprising for a patient with tuberculous peritonitis to walk around with so much abdominal distention without more fever and more constitutional symptoms. Moreover, I should expect the effusion to have had a higher specific gravity, a higher protein content and more of the characteristics of an exudate.

Could the disease have been lupus erythematosus with polyserositis? No other manifestations of lupus erythematosus were present, and the clinical picture was not that of this disease.

Now I come to the group that I have classed for special consideration. Two possibilities that I think should be seriously entertained are interference with the return of blood and with the drainage of the peritoneal cavity because of constrictive pericarditis, and thrombosis of the hepatic veins. Both those conditions would lead to the accumulation of ascites with the characteristics of a transudate. There may be pain as a result of hepatomegaly with distention of the capsule. The pain is usually not in the lower abdomen, however, with either of these two conditions. Thrombosis of the hepatic veins is rare. It may be associated with either cirrhosis of the liver, which this patient may have had in the background, or with a malignant neoplasm. Certainly, there were many findings to suggest a malignant neoplasm, with inflammation and inflammatory involvement of the veins or with thrombosis. I think at this point I might look at the x-ray films.

*Assistant in medicine, Massachusetts General Hospital.

DR. RICHARD V. WILSON: The diffuse haziness of the abdomen caused by the ascitic fluid obscures the kidneys, the liver edge and the spleen. The psoas shadows are poorly seen, the left being better outlined than the right. I do not think that this means anything. The time between the films is four days; in that interval the dilatation of the bowel increased greatly. All portions of the bowel, however, are dilated. The barium-enema examination was done because no air was seen in the large bowel beyond the splenic flexure, but the entire large bowel fills back to the cecum. There is a small amount of fluid in the right pleural cavity, which probably accounts for the shadow across the right-midlung field, although it could be due to thickened pleura in the horizontal fissure. The heart is transverse in position; the left ventricle is somewhat prominent. The aorta is quite tortuous.

DR. CALKINS: Was there a subsequent film?

DR. WILSON: Another film was taken a day or two later, but the diaphragm is higher. The right leaf of the diaphragm is higher than usual, but both leaves are elevated.

DR. CALKINS: The patient must have had a considerable hepatomegaly if the liver edge was palpable. Was there evidence of calcification in the pericardium? None was mentioned, and I do not see any.

DR. WILSON: I do not either. There is calcification in the aorta.

DR. CALKINS: Is there evidence of congestion of the lungs?

DR. WILSON: No.

DR. CALKINS: The mediastinum does not look particularly wide, but I think this is difficult to interpret in this case.

DR. WILSON: The mediastinal shadow is wide, but that could be caused by the tortuosity of the aorta. I do not think there is anything there.

DR. CALKINS: I am not given any assistance in the diagnosis of constrictive pericarditis from the x-ray films, but that does not exclude this possibility. The electrocardiogram does not indicate anything to me other than the effect of digitalis, which I assume the patient was still receiving at that time. I should not expect the manifestations of constrictive pericarditis to develop as rapidly as the symptoms described in this case. Therefore, if one were going to pick venous obstruction, one had better choose thrombosis of the hepatic veins, which would be much more rapid in its onset. I think that I should like to regard this possibility as an important one, though I am disturbed by the cloudiness of the ascitic fluid. The cloudy fluid suggests certain other possibilities.

Could it have been acute pancreatitis? No. The patient did not have enough constitutional manifestations for the ascites to have been associated with acute pancreatitis.

Could it have been peritoneal seeding from a neoplasm? Many features of this case point to a neoplasm, particularly the cachexia and the relatively rapid development of the manifestations of disease. Certainly, peritoneal seeding may result in cloudy ascitic fluid. The fact that tumor cells were not found in the fluid does not exclude this condition. Pseudomyxoma peritonei, from the appendix or some other site in the intestinal tract, is a special form of tumor, characterized by accumulation of ascitic fluid, which has a cloudy appearance. This is not as malignant or as incapacitating an ailment as carcinomatosis. The course is seldom as rapidly downhill as in this case.

Could the cloudy ascites have been chylous because of obstruction of the thoracic duct from carcinomatosis or lymphoma? I think that is a very reasonable possibility. Patients with chylous ascites are able to walk around without too much incapacity.

The main possibilities, therefore, are cirrhosis, which I rule out as the main diagnosis because of the lack of stigmas on physical examination, constrictive pericarditis, or thrombosis of the hepatic veins, which would not be expected to produce a cloudy ascites, and carcinomatosis with obstruction to the thoracic duct. Of these I favor the last as the cause of the ascites. The most likely primary site is the stomach.

How cloudy was the fluid?

DR. GEROLD L. SCHIEBLER: The first time that we did the paracentesis the fluid was quite cloudy; some people accused us of being in the bowel, but we were not. The second time we did the paracentesis, because the patient went into pulmonary edema on the day of death, it seemed considerably clearer. I cannot explain why it was so cloudy that day.

DR. CALKINS: That pulmonary edema does not fit into my calculations, nor had I realized that he had pulmonary edema. It was not mentioned in the protocol.

DR. SCHIEBLER: When you evaluate the problem of the pulmonary edema, you must realize that this patient spent two months in bed with hardly any treatment before he came into the hospital.

DR. CALKINS: You are enticing me to leave my line of thinking and choose a diagnosis that I previously excluded—that is, that the heart was predominantly involved. I shall not be dissuaded.

DR. JOHN R. DAVID: One other problem was whether the patient had dilatation of the bowel. In the middle of the night we took him down to the Department of Radiology to rule out bowel obstruction. I do not think we explained the obstruction very well on the basis of carcinoma. We ruled out an obstructive mass.

DR. CALKINS: No; you did not, and I do not. However, it is not uncommon for distention of the bowel to occur secondary to the prolonged ascites of carcinomatosis. Distention is not common if the

ascites is an ordinary transudate, but if it is of an irritative nature distention is apt to occur. Dr. Kranes looks skeptical.

DR. ALFRED KRANES: I should like to take issue with that, because the syndrome of paralytic ileus is not uncommon as a terminal event in patients with cirrhosis of the liver; it is often precipitated by a paracentesis and is usually associated with an extremely low serum sodium. The exact mechanism of the ileus is not known. Many of these patients have been operated on for intestinal obstruction. I think that everything in this case can be explained on a basis of Laënnec's cirrhosis, although there are certain atypical findings.

DR. CALKINS: I like your comment that dilatation occurs in cirrhosis. This does not alter my argument. I think that cirrhosis is a perfectly reasonable possibility, but I cannot commit myself to that as the primary diagnosis since none of the accompanying clinical manifestations were described.

DR. KRANES: When an old man has jaundice and ascites, cirrhosis is so much more likely than anything else that, on a statistical basis, one is more likely to be correct—granted that statistics are not always reliable in a clinicopathological conference. The serum albumin was low, and the bilirubin elevated. I do not see anything inconsistent with such a diagnosis.

DR. CALKINS: I agree that the patient had parenchymal liver disease, but I do not think cirrhosis was the cause of the ascites.

A PHYSICIAN: How do you explain the abdominal pain, Dr. Kranes?

DR. KRANES: By the paralytic ileus.

DR. CALKINS: He came in with that.

DR. KRANES: Did he not have gaseous dilatation of the abdomen when he first came in?

DR. SCHIEBLER: Only fluid without too much gas.

DR. KRANES: The bowel contained a mixture of fluid and gas. Is not that bowel distended on the first film, Dr. Wilson?

DR. WILSON: Yes; even on the first film there is some dilatation of the small bowel, but not much.

DR. KRANES: Patients with cirrhosis do have unexplained abdominal pain even without ileus. I think that the patient under discussion had ileus in addition.

DR. LAWRENCE H. WARBASSE: I should like to suggest that recurrent right-upper-quadrant and protracted abdominal pain is quite often seen in cirrhosis. The liver-function tests are consistent with that diagnosis. Such patients often have a low serum sodium and sometimes a chronic potassium insufficiency, which may be the reason that the patient under discussion had greatly dilated loops of bowel. As Dr. Kranes has indicated, several investigators have shown that peripheral vascular collapse, water intoxication, coma and death may follow a large paracentesis, especially in patients with a pre-existing hyponatremia. These defects may be rectified by hypertonic saline solution. I do not wish to analyze the total clinical situation in this case, but I should like to point out that this patient died two hours after the final paracentesis. I should venture to say that, whatever else he had, he did have cirrhosis and paralytic ileus and that he died of physiologic derangements after the tap.

DR. CALKINS: I think the reasoning would apply if there were ascites of other etiology.

DR. JACOB LERMAN: I should like to suggest, in addition to what Dr. Kranes said about paralytic ileus, that in cirrhosis idiopathic peritonitis also occurs as a complicating factor terminally. That might explain the cloudy ascites with a high white-cell count and high neutrophil percentage.

DR. WARBASSE: Pulmonary edema sometimes is seen terminally in cirrhosis. I do not know why it occurs.

CLINICAL DIAGNOSES

Widespread malignant neoplasm of abdomen.
Arteriosclerotic heart disease, with congestive heart failure.
Pulmonary edema.

DR. EVAN CALKINS'S DIAGNOSIS

Carcinomatosis, with involvement of thoracic duct.

ANATOMICAL DIAGNOSES

Acute cholecystitis, with cholelithiasis.
Ascites, with focal acute peritonitis.
Bronchopneumonia.
Laënnec's cirrhosis of liver, mild.
Cardiac hypertrophy, hypertensive type.
Pulmonary edema.
Hydrothorax, bilateral, slight.

PATHOLOGICAL DISCUSSION

DR. WINFIELD S. MORGAN: At autopsy the peritoneal cavity contained about 2500 ml. of cloudy, yellowish fluid. In the right upper quadrant there were a moderate number of relatively recent adhesions. The greater omentum was adherent to the gall bladder, and there was a small pocket of pus in this region. The gall bladder itself was distended with about 150 ml. of purulent material and contained numerous small, greenish calculi. The common duct was of normal caliber and was free of stones. Portions of the gall bladder were greenish and covered with exudate, but careful examination did not disclose a perforation. Microscopical examination revealed an acute cholecystitis superimposed on an old chronic process.

The liver was within the limits of normal weight, about 1400 gm., and was finely granular. Microscopically, it demonstrated an early but definite portal cirrhosis. The spleen was within the limits of normal weight, 200 gm. Each of the pleural

cavities contained 150 cc. of clear serous fluid. The lungs were heavy, congested and edematous and contained numerous areas of bronchopneumonia. The heart was moderately increased in weight for this small man, 400 gm., and showed a definite hypertrophy of the left ventricle; the wall measured 20 mm. in thickness. The coronary arteries, however, were only minimally sclerotic, and the microscopical sections of the myocardium were not abnormal.

I also find it difficult to tie this case up into a nice, neat package, and I think we are at somewhat of a disadvantage in that we do not have all the details of the past medical history. I believe the immediate cause of death was the bronchopneumonia and the acute cholecystitis occurring in an elderly, debilitated man. Although there was no history of hypertension, the gross appearance of the heart strongly suggests that he had hypertension in the past, and I should assume that the previous bouts of congestive heart failure were on that basis. I find it extremely difficult to evaluate the role the liver played in the patient's difficulty, because the cirrhosis, although present, was not severe and ordinarily we should not expect cirrhosis of this degree to bother a person very much. I am not sure that we have explained the ascites although it may have been the result of a combination of liver disease and cardiac insufficiency in an elderly patient.

DR. ROBERT L. BERG: How do you explain the pocket of pus about the gall bladder?

DR. MORGAN: We assumed that there was seepage through the wall of the gall bladder to which it was adjacent.

DR. BERG: I was pleased that Dr. Calkins made the same sort of diagnosis that we made on the ward. This was a most difficult case in which to reach a satisfactory diagnosis. In retrospect I suppose we might speculate that an elderly, debilitated patient, who failed to exhibit fever and local tenderness in response to an acute infection, might also be expected to fail to produce an optimal inflammatory response as evidenced by the type of ascitic fluid found. He was, perhaps, an example of overrationalized treatment in that we withheld both antibiotics and surgery. Both were considered from day to day with the help of the surgeons, but we believed there was no indication to proceed with either one of these. Actually, if we had been more venturesome, he might have survived even though his general condition was very poor.

MASSACHUSETTS PHYSICIANS ART SOCIETY

43. Mill on the River

Exhibited at Annual Meeting, Massachusetts Medical Society, 1955

Oil Painting by

ELIZABETH Z. KLEINMAN, M.D.

Assistant, Department of General Practice, New England Hospital

The New England
Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY

OWNED BY THE SOCIETY AND
PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE
COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. Richard E. Alt, M.D.
Oliver Cope, M.D. James M. Faulkner, M.D.

Joseph Garland, M.D., EDITOR
ASSOCIATE EDITORS
Thomas H. Lanman, M.D. Donald Munro, M.D.
Theodore H. Ingalls, M.D.

Robert O'Leary, ASSISTANT EDITOR
Milton C. Paige, Jr., BUSINESS MANAGER

EDITORIAL BOARD
Henry R. Viets, M.D. Benjamin Castleman, M.D.
Dwight O'Hara, M.D. J. Englebert Dunphy, M.D.
Fletcher H. Colby, M.D. Robert W. Buck, M.D.
Robert L. Goodale, M.D. Herrman L. Blumgart, M.D.
Chester M. Jones, M.D. Frank N. Allan, M.D.
Harvey R. Morrison, M.D. Harvey A. Kelly, M.D.
Maxwell Finland, M.D. Langdon Parsons, M.D.
Vernon P. Williams, M.D. Mark Aisner, M.D.

MANUSCRIPTS, including references or bibliography, should be typewritten double spaced and submitted as original copy. References should conform to the style of the *Quarterly Cumulative Index Medicus* (listing name and initials of author, title of article, journal, volume number, first and last pages and year), and should be cited numerically in the order in which they appear in the text; the number should be limited to the absolute minimum.

ILLUSTRATIONS are reproduced as half tones and zinc etchings. Photographs must be distinct, and drawings done in black ink on white paper and each properly labeled.

MATERIAL printed in the *New England Journal of Medicine* is covered by copyright. Articles are accepted for consideration with the understanding that they are contributed for publication solely in this journal. The *Journal* does not hold itself responsible for statements made by any contributor.

MATERIAL, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

COPY for advertisements is accepted by the advertising committee of the *Journal* on the basis of the apparent quality and usefulness of the product and the manner of its presentation. Proprietary names of pharmaceutical products must be accompanied by the chemical, or generic or official names, and the quantity of all active substances and the recommended dose must be stated. Copy should be factual, conservative and in good taste.

ALTHOUGH it is believed that all advertising material accepted conforms to ethical medical standards, acceptance does not imply endorsement by the *Journal*.

SUBSCRIPTION TERMS: $8.00 per year in advance, postage paid, for the United States (interns and medical students, $5.00 per year); Canada, $9.00 per year (Boston funds); foreign, $10.50 per year. Long-term rates: United States, 2 years $15.00, 3 years $22.00; Canada, 2 years $17.00, 3 years $25.00; foreign, 2 years $20.00, 3 years $29.50.

MICROFILM volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

HISTOPLASMOSIS: RECENT DEVELOPMENTS

THE subject of histoplasmosis of the lung was reviewed in December, 1954, by Schwartz[1] and early in 1955 by Smith.[2] Although the disease at that time had been recognized in 22 countries, more than four fifths of the authentic cases have been reported from the United States, where this disease has aroused interest because of possible confusion of its manifestations with those of tuberculosis, particularly in roentgenographic chest surveys. Next to the United States, the disease appears to be most frequent in Mexico and in Central and South America, but it has been recognized in all parts of the world. In this country it occurs chiefly in the Mississippi, Missouri and Ohio river valleys. Recently, the causative organism, *Histoplasma capsulatum*, was isolated from a case of histoplasmosis in a dog in the Pacific Northwest — apparently for the first time in that area.[3]

Emmons and his co-workers[4,5] recently reported the isolation of *H. capsulatum* from a large number of animals in Loudoun County, Virginia, during the past eight years; they could demonstrate the fungus in about a third of all dogs, a fifth of all cats and about 3 per cent of rats, opossums, foxes and woodchucks, but only once in mice.[4] By mouse inoculation of fresh or deep-frozen peribronchial lymph nodes, they succeeded in finding the fungus in more than half the dogs in that area; they attributed the failure to isolate *H. capsulatum* by direct culture to the frequency of contamination of this tissue by saprophytic fungi and occasionally bacteria.[5]

Recent studies in Minnesota have indicated high rates of infection in certain households in sharply localized areas where the environmental conditions were particularly suitable for survival of the fungus. This explained the higher rates of infection among farm dwellers as compared with those living in the nearby villages.[2,6] In Virginia, household epidemics have been described in farm families associated with the demonstration of infection in domestic animals.[4] Acute cases resembling pneumonia have been recognized as the result of infection acquired from the sifting of soil that contains the fungus.[7] Chicken houses appear to provide a proper environment for the survival and spread of the fungus, which has been found in the air in and outside them.[8] High acidity of the soil under such conditions was found to be an important factor.[9]

At the Fourteenth Conference on the Chemotherapy of Tuberculosis of the Veterans Administration, Army and Navy, evidence was presented that emphasized the importance of histoplasmosis in tuberculosis sanatoriums. Sutliff and Campbell[10] performed serologic tests with antigens prepared from three fungi and discovered that 24 per cent of 300 patients selected at random from the Infectious Diseases, Pulmonary Disease and Thoracic Surgery Sections of the Veterans Administration Hospital in

Memphis, Tennessee, yielded evidence of either histoplasmosis, North American blastomycosis or coccidioidomycosis. Brasher and Furcolow,[11] at the Missouri State Sanatorium, discovered that about 2.2 per cent of patients considered to have advanced tuberculosis, with cavities in their lungs, actually had active histoplasmosis, proved by examination of resected specimens of lung or by cultivation of the fungus; about 5.3 per cent probably had this disease as evidenced by positive skin tests with histoplasmin or by the discovery of specific antibodies in the blood. They estimated that about 1300 such cases would be found in the areas of high prevalence of histoplasmosis.

The treatment of histoplasmosis remains unsatisfactory. A case of localized histoplasmosis of the hard palate and gingiva apparently responded favorably to treatment with 2-hydroxystilbamidine.[12] Satisfactory data on the effects of new fungistatic agents in this disease are still lacking. Many healed or healing cases are recognized after resection of pulmonary lesions, often suspected of being tuberculous.[13] As with many other infections due to bacteria, viruses, fungi or yeasts,[14] the possibility of activating latent infection or increasing the dissemination of histoplasma infection widely throughout the body during treatment of other diseases with cortisone or other adrenocortical hormones must always be considered; this has recently been demonstrated in experimental histoplasmosis in guinea pigs.[15] The danger is greatest when the hormone treatment is prolonged or when large doses are used, and, in such cases, the risk is not avoided and may actually be increased by the added use of the available antibiotics.

References

1. Schwartz, B. Histoplasmosis of lungs. *Arch. Int. Med.* **94**:970-994, 1954.
2. Smith, R. T. Histoplasmosis: review with epidemiological and clinical study of outbreak occurring in Minnesota. *Journal-Lancet* **75**:83-100, 1955.
3. Eby, C. H., and Ringen, L. M. Canine histoplasmosis in Pacific Northwest. *J. Am. Vet. Med. A.* **127**:250, 1955.
4. Emmons, C. W., et al. Histoplasmosis: proved occurrence in inapparent infections in dogs, cats and other animals. *Am. J. Hyg.* **61**:40-44, 1955.
5. Emmons, C. W., and Rowley, D. A. Isolation of *Histoplasma capsulatum* from fresh and deep-frozen peribronchial lymph nodes of dogs by mouse inoculation. *J. Lab. & Clin. Med.* **45**:303-307, 1955.
6. Sachs, D., Smith, R. T., Fleming, D. S., and Furcolow, M. L. Prevalence of positive reactions to tuberculin and histoplasmin in rural Minnesota county. *Am. J. Hyg.* **62**:43-53, 1955.
7. Kier, J. H., Campbell, C. C., Ajello, L., and Sutliff, W. D. Acute bronchopneumonic histoplasmosis following exposure to garden soil. *J.A.M.A.* **155**:1230-1332, 1954.
8. Furcolow, M. L., Menges, R. W., and Larsh, H. W. Epidemic of histoplasmosis involving man and animals. *Ann. Int. Med.* **43**: 173-181, 1955.
9. Zeidberg, L. D., Ajello, L., and Webster, R. H. Physical and chemical factors in relation to Histoplasma capsulatum in soil. *Science* **122**:33, 1955.
10. Sutliff, W. D., and Campbell, C. C. Serologic screening for systemic mycoses. *Tr. Conf. Chemother. Tuberc.* **14**:285-288, 1955.
11. Brasher, C. A., and Furcolow, M. L. Chronic cavitary histoplasmosis as problem in tuberculosis sanatoria. *Tr. Conf. Chemother. Tuberc.* **14**:288-294, 1955.
12. Nejedly, R. F., and Baker, L. A. Treatment of localized histoplasmosis with 2-hydroxystilbamidine. *Arch. Int. Med.* **95**:37-40, 1955.
13. Puckett, T. F. Pulmonary histoplasmosis. *Am. J. Surg.* **90**:92-100, 1955.
14. Kass, E. H., and Finland, M. Adrenocortical hormones in infection and immunity. *Ann. Rev. Microbiol.* **7**:361-388, 1953.
15. Vogel, R. A., Michael, M., Jr., and Timpe, A. Cortisone in experimental histoplasmosis. *Am. J. Path.* **31**:535-543, 1955.

DEPTH AND BREADTH OF MEDICAL EDUCATION

Medicine, when it broke away from the domination of the "medicine-man" centuries ago, rejected preoccupation with magic and the metaphysical to concern itself with scientific studies of the human body and the effects of an indifferent environment upon it. To understand this environment broadly some knowledge of its minutiae was necessary. The microscope revealed details of human anatomy and cellular reactions of the body to the microcosm that surrounds each man — inside and out. Biochemistry brought molecular dissection of the internal milieu and an understanding of foods and fluids; but a relatively satisfactory understanding of the rise and fall of gastric hydrochloric acid provided a rather empty explanation of why human beings actually got peptic ulcer and which of them hated their bosses or their jobs or both. Medicine set about to consolidate its new gains and to re-examine what it had left behind long ago. It readmitted the psychical and even much of the mystical; psychiatry and psychosomatic medicine stepped back in to give further dimension to the mechanical robot with peptic ulcer. The social sciences supposedly completed the curriculum necessary to train the rounded physician to take care of the whole man in a brave new world.

Today that physician or his alter ego, the colleague to whom the patient may be referred when the going gets too specialized, is supposed to be able to keep the patient's athlete's foot under control along with his Oedipus complex; and to help him cope with intemperate urges to smoke, drink, cohabit and eat too much — to burn the candle at both ends, to work too hard from Monday to Friday, to play too much golf on Saturday and to pass the plate too readily on Sunday.

With such considerations in mind the medical schools have given a new look at their new curriculum. The procedure is vaguely reminiscent of the retooling that is necessary when a new model car comes off the assembly line. The medical graduate in 1957 will have the benefit of all the new changes. He may have had several families in medical school that were all his own — from tonsillitis in the children right down to the last breech delivery of the mother and the father's peptic ulcer. By the time he has graduated he will have had his eyes opened widely to psychiatric, economic, social and cultural components of a disease.

Considering that he will already have had basic sciences and a liberal education at an undergraduate level, then anatomy, embryology, biochemistry, pharmacology and the other medical sciences in the first two years of graduate school, and all the specialties in addition to the synthesis that is general practice, his erudition will be great indeed. He would seem to be ready for practice. The only difficulty is to as-

semble experience and to confront a macrocosm that looms up every bit as large as the world of the microscope in the times of van Leeuwenhoek, Pasteur, Koch and Virchow. The total assignment cannot be prepared in one person's lifetime. In addition many of the global factors are but dimly seen and not subject as yet to a scientific approach or control.

VITAMINS, ANTIBIOTICS AND INFECTIONS

It is well known that the use of antibiotics, particularly those having a wide spectrum of antimicrobial activity, may be accompanied by untoward effects, some of which may simulate signs and symptoms of certain specific vitamin deficiencies. On the other hand, there is little if any proof that true vitamin deficiencies may result from the ingestion of these antibiotics during ordinary usage in the treatment of acute infections in persons not already suffering from malnutrition. In particular, there is almost no acceptable and undisputed evidence that the untoward effects attributed to the broad-spectrum antibiotics can be either prevented or relieved by administration of vitamins, either individually or in combinations.

A critical survey of the relevant literature bearing on this subject by a competent authority in the field is presented elsewhere in this issue of the *Journal*. In the introduction to her review, Dr. Goldsmith points out the highly conjectural nature of the report on *Therapeutic Nutrition* that was the basis not only for the principle upon which the combination of antibiotics and vitamins was proposed but also for the very details of the components of the mixture of vitamins actually formulated for the purpose. It is for this reason that the Food and Nutrition Board, of which Dr. Goldsmith is now a member and chairman of its Committee on Dietary Allowances, has decided to withhold further printing of that report pending critical reconsideration of the subject.

The Committee on Therapeutic Nutrition of the Food and Nutrition Board, with the full prestige and authority of the National Academy of Sciences and the National Research Council, originally sponsored and authorized the publication of the report on *Therapeutic Nutrition* "in the hope that it will draw attention to and stimulate research on the potentialities of *Therapeutic Nutrition*." According to the foreword by the sponsors "the report attempts to summarize what appears to be about as reasonable a consensus as can be assembled." It also goes on to say that "The [Food and Nutrition] Board does not consider this report to contain many final answers but expresses the hope that it may engender proper consideration of nutritional therapy in accelerating the natural process of recovery from disease or injury."

A careful study of this and other reports indicates that the vitamin requirements of man are really not known. In particular, the report states clearly that "vitamin requirements under stress have never been completely determined." Nevertheless, it states that "on an empirical basis, it is common practice to administer up to ten times the recommended normal daily allowance for vitamins under stress situations."

The implication seems clear or at least is readily open to the interpretation that the purpose of the report was to stimulate interest in the use of nutritional therapy, — which for most people would mean vitamins or artificially compounded mixtures of vitamins and other nutritional elements, — particularly during infections and in other stressful situations. It is little wonder, then, that this was also interpreted as a mandate to manufacturers of vitamins and pharmaceuticals to supply the elements recommended and in the amounts suggested by this report. Nor can such manufacturers be blamed for exploiting the authoritative position of this report and of its sponsors in advertising and promoting their products.

The controversial nature of these recommendations and the conflicting data concerning both the possible value and the potential harm from the use of some of the nutritional elements, in the amounts recommended and under a variety of different situations, was not adequately brought out in the report on *Therapeutic Nutrition*. These are now assembled and assessed by Dr. Goldsmith in her review, which properly concludes that there is no magic formula that can relieve the practicing physician of detailed analysis of all facets of the patient's nutritional state. Each patient represents an individual problem, and although the importance of maintaining adequate nutrition during the course of infections and in other diseases is now being recognized, much remains to be learned about what constitutes adequate nutrition. Many of the perplexing problems concerning the relation between nutrition and infection and in the effects of antibiotics offer a challenge to scientists working in this field. Their solution should put therapeutic nutrition on a rational rather than a conjectural basis.

It might be added that this incident, as well as similar experiences in other fields, more than justifies the cautious attitude of the more conscientious and critical among scientists toward generalization and rapid exploitation of their discoveries and contributions. The scientist is thus often faced with a serious dilemma: he is willing and anxious to reveal his discoveries so that they may be freely discussed and evaluated and used as a basis for further advances; unfortunately, in so doing, he also permits the revelations to be used prematurely by less scrupulous and less critical persons, some of whom are quite willing to exploit both the discoveries and the scientists.

MASSACHUSETTS PHYSICIAN

THE *Norfolk Medical News* has announced that, beginning with the issue of January, 1956, its name has been changed to *Massachusetts Physician*. Attention is called to the fact that the *News*, although sponsored by the Norfolk District Medical Society, is and has been a publication with a statewide circulation. The *News*, as is well known, has been regularly sent without charge to the total membership of the Massachusetts Medical Society.

At the New Hampshire Lunatic Asylum recently, a furiously insane inmate, while struggling with two keepers, suddenly dropped dead, probably in consequence of a rush of blood to the head.

Boston M. & S. J., *Jan. 31, 1855*

MASSACHUSETTS MEDICAL SOCIETY

RALPH RICKER STRATTON

Ralph Ricker Stratton died on November 27, 1955. For over half a century he practiced his profession as a doctor who loved to get sick people well. He had a heart as well as a head and hands. He brought to many a bedside in home and hospital the charm of manner that comes from a blending of the art with the science of medical practice. He never spared himself. To him a summons to attend someone who was ill was a duty never to be shirked. He was a good doctor.

Dr. Stratton belonged to the Massachusetts Medical Society for over fifty years. He served it loyally and without stint. Of him it may be said that he gave in full measure to the Society he loved as much as, if not more than, he received. He was long a councilor from his district of Middlesex East, and for many of those years he was that district's nominating councilor. He liked that assignment, for, as he himself put it, he preferred to be maker of kings rather than be king himself. His outstanding contribution to the Massachusetts Medical Society, however, was as a member, and then as chairman, of the Committee on Ethics and Discipline. To that office he brought dignity, kindness and a judicial temperament that safeguarded the rights of those who became the concern of that committee, and at the same time sternly upheld the standards of conduct demanded of physicians.

Ralph Stratton was above all a gentleman. If ever angered, he never showed it by either deed or word. Courteous always, ever mindful of the needs and rights of others he was of the old school in which he was bred, holding fast to its virtues, not narrowly but with a mind receptive to values of changing times. Those who knew him at all, even slightly, were quick to recognize the sterling worth of the man, and all whose good fortune it was to know him intimately count their lives enriched by the abiding friendship it was Ralph Stratton's nature to give.

A.G.R.

COMMITTEE ON MATERNAL WELFARE

INTRA-ABDOMINAL HEMORRHAGE

A thirty-year-old gravida III, para II, died from a rupture occurring with an ectopic pregnancy.

She was first seen by her own physician eleven days after the onset of a supposedly normal menstrual period, which, however, had become abnormal in that intermittent bleeding continued almost daily. Nothing was found on examination, but bleeding recurred six and nine days later, when a pelvic mass was found and the patient was admitted to the hospital (that is, twenty-five days after the onset of a presumably normal period but six days after the onset of severe, steady pelvic pains).

On admission physical examination was negative except for a tender mass in the left adnexa and anemia (red-cell count of 3,390,000, with a hemoglobin of 9.3 gm. per 100 ml.). The patient was in good condition, with a blood pressure of 110 systolic, 74 diastolic; her blood was immediately typed and crossmatched, and she was prepared for surgery.

For reasons that do not appear in the record, a four-hour delay occurred between admission and the start of nitrous oxide, oxygen and Pentothal anesthesia. Under anesthesia, a pelvic examination and dilatation and curettage were performed, during which the patient suddenly collapsed, with complete disappearance of pulse and blood pressure in spite of the fact that she was receiving a blood transfusion before the onset of anesthesia. Immediately afterward, it was thought that the heart sounds had entirely stopped, and, therefore, a thoracotomy was performed and cardiac massage instituted. These measures resulted in the return of some circulation, and the blood pressure rose to 90 systolic, 60 diastolic, as additional blood was given. However, four and a half hours after the onset of anesthesia, she died without ever having had her abdomen opened.

Autopsy revealed a rupture with ectopic pregnancy, with massive intra-abdominal hemorrhage to the extent of at least 1500 ml. of blood.

This case was classified as a preventable death, the primary cause, of course, being intra-abdominal hemorrhage and the primary avoidable factor being delay. The patient presented a history certainly suggestive of ectopic pregnancy, and it seems that the diagnosis was hardly in doubt at the time of admission. It is difficult to understand why the treatment was delayed for four hours after she had been ad-

mitted and the blood typed and crossmatched. Familiar as everyone is with the delays occurring in any hospital and its operating suite, one is inclined to believe that extraneous factors, such as other surgery in progress at the time, may have prevented the surgeon from treating her as soon as he would have liked. If that is so, the hospital authorities contributed heavily to the patient's death. Patients with the presumptive diagnosis of ectopic pregnancy should be given a priority over all other cases scheduled. One cannot quarrel in retrospect with the diagnosis of cardiac arrest, but it seems possible that this represented nothing more than the profound shock that followed extremely sudden and severe abdominal hemorrhage. Pelvic examination presumably ruptured the ectopic conceptus, and it seems clear that a laparotomy done without prior curettage would probably have corrected the condition before the situation became critical. These factors are admittedly a matter of judgment and much more easily criticized in retrospect than elucidated during the procedure.

One further comment seems indicated—namely, that this case falls into a group of patients dying from hemorrhage whose underlying secondary anemia gravely aggravates their emergency condition when it occurs. Obviously, this had been taken into account, for blood was started in advance—a fact that is heartily endorsed. However, the use of Pentothal anesthesia for a patient with anemia, particularly of this severe degree, is deplored.

JOHN FIGGIS JEWETT, M.D.
Chairman

CORRESPONDENCE

HYPOGLYCEMIA AND PANCREATIC TUMORS

To the Editor: Too late for inclusion in our paper, "Marked Hypoglycemia Associated with Nonpancreatic Tumors," published in the January 5 issue of the *Journal*, Dr. Simon and I discovered the important paper by Sillern et al. in *Diabetes* (3:133-140, 1954), in which they reported 2 large tumors associated with hypoglycemia. They also reviewed the literature. One of their cases was originally thought to be a neurofibrosarcoma of the right hemidiaphragm, and the other case, thought to be a fibrosarcoma, was found to be a tumor occupying much of the abdominal cavity. Both patients were completely relieved of hypoglycemia after removal of the tumors. The histology of these tumors was very similar to that in our case. No insulin assays were done on their tumors. An occasional area with blue granules was seen in their sections after a Gomori stain. Our case revealed no blue granules with the Gomori stain. Chiefly on the basis of the few blue granules, Sillern et al. believed that the tumors were low-grade islet-cell carcinomas. There were no other histologic features that suggested islet-cell tumor.

RICHARD S. SILVIS
Captain (MC) USN
Chief, Surgical Service
United States Naval Hospital
Oakland, California

BOOK REVIEW

The Diseases of Occupations. By Donald Hunter, M.D., F.R.C.P. 8°, cloth, 1046 pp., with 435 illustrations. Boston: Little, Brown and Company, 1955. $20.00.

Dr. Donald Hunter, physician and director of the Department for Research in Industrial Medicine at the London Hospital, England, has written a most scholarly treatise on health in industry. The first part is devoted to an interesting résumé of the poor health conditions of the working man and of social reforms in the industrial revolution of the nineteenth century. The great improvements that have occurred in the twentieth century are vividly contrasted. This is particularly interesting, for the British were the pioneers in industrial health.

After the first 200 pages the author turns to the obvious diseases produced by industry, describing not only the origin and course and treatment of the disease but also the working habits that produce it, as well as the technics for prevention. The book is long enough (1046 pages) to give clear and comprehensive discussions. Not only is it well written and adequately inclusive, but also it has a readable style that holds one's attention.

The publishers have done an excellent job, for the volume is beautifully printed and has profuse and excellently reproduced illustrations.

This is by far the best textbook and reference book on industrial disease that the reviewer has seen. This truly remarkable compilation should be welcomed with enthusiasm by anyone interested in the medical aspects of industry. When one considers how many hours are spent on jobs that may involve hazards to health, one realizes that many besides physicians and medical students could read this book with profit.

JOSEPH C. AUB, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Bronchus und Tuberkulose: Bronchoskopische und bronchographische Untersuchungen der Bronchen bei der Tuberkulose. By Dr. Med. A. Huzly, Sanatorium Schillerhöhe der Lva. Württemberg, Stuttgart-Gerlingen; and Dr. Med. F. Böhm, Heilstätte Überruh der Lva. Württemberg, Isny. 4°, cloth, 138 pp., with 258 illustrations. Stuttgart: Georg Thieme, 1955. DM 57.- $13.55. (Distributed by the Intercontinental Medical Book Corporation, New York City.)

The Lung: Clinical physiology and pulmonary function tests. (Based on the 1954 Beaumont Lecture.) By Julius H. Comroe, Jr., M.D., professor of physiology and pharmacology, Graduate School of Medicine, University of Pennsylvania; Robert E. Forster, II, M.D., associate professor of physiology and Lowell M. Palmer Senior Fellow, Graduate School of Medicine, University of Pennsylvania; Arthur B. Dubois, M.D., assistant professor of physiology, Graduate School of Medicine, University of Pennsylvania; William A. Briscoe, M.D., associate in physiology, Graduate School of Medicine, University of Pennsylvania; and Elizabeth Carlsen, A.B., Isaac Ott Fellow in Physiology, Graduate School of Medicine, University of Pennsylvania. 8°, cloth, 219 pp., with 57 illustrations and 14 tables. Chicago: Year Book Publishers, Incorporated, 1955. $5.50.

Clinical Disorders of Hydration and Acid-Base Equilibrium. By Louis G. Welt, M.D., professor of medicine, Department of Medicine, University of North Carolina. 8°, cloth, 262 pp., with tables. Boston: Little, Brown and Company, 1955. $6.00.

Lehrbuch der Auskultation und Perkussion. By Priv.-Doz. Dr. Med. K. Holldack, Med. Univ.-Poliklinik, Heidelberg. With a preface by Prof. Dr. Med. Curt Oehme, Heidelberg. 8°, cloth, 195 pp., with 83 illustrations. Stuttgart: Georg Thieme, 1955. DM 27.- $6.40. (Distributed by the Intercontinental Medical Book Corporation, New York City.)

The Tubercle Bacillus in the Pulmonary Lesion of Man: Histobacteriology and its bearing on the therapy of pulmonary tuberculosis. By Georges Canetti, M.D., director of laboratory, Pasteur Institute, Paris. With a foreword by René J. Dubos and Walsh McDermott, M.D. 8°, cloth, 226 pp., with 48 figures and 10 tables. New York: Springer Publishing Company, Incorporated, 1955. $8.50.

Pomp and Pestilence: Infectious disease, its origin and conquest. By Ronald Hare, M.D., professor of bacteriology in the University of London at St. Thomas's Hospital Medical School. 12°, cloth, 224 pp. New York: Philosophical Library, Incorporated, 1955. $5.75.

The Subnormal Mind. By Sir Cyril Burt, D.Sc. Third edition. 8°, cloth, 391 pp. London: Oxford University Press, 1955. $5.00. (University of London, Heath Clark Lectures, 1933, delivered at the London School of Hygiene and Tropical Medicine.)

Receptors and Sensory Perception: A discussion of aims, means, and results of electrophysiological research into the process of reception. By Ragnar Granit, director of the Nobel Institute for Neurophysiology and professor of neurophysiology, Karolinska Institutet, Stockholm. 8°, cloth, 369 pp., with 145 illustrations. New Haven: Yale University Press, 1955. $5.00.

Fear Strikes Out: The Jim Piersall story. By Jim Piersall and Al Hirshberg. 8°, cloth, 217 pp. Boston: Little, Brown and Company, 1955. $3.50.

Chemistry and Biology of Pteridines. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Margaret P. Cameron, M.A., A.B.L.S. 8°, cloth, 425 pp., with 143 illustrations and diagrams. Boston: Little, Brown and Company, 1954. $8.00. (*Ciba Foundation Symposium.*)

Le potassium et la vie. By Alain Reinberg, D.S., M.D. 12°, paper, 126 pp., with 10 illustrations and 9 tables. Paris: Presses Universitaires de France, 1955. (*"Que sais-je?" Le point des connaissances actuelles.*)

Modern Treatment Yearbook 1955: A yearbook of diagnosis and treatment for the general practitioner. Edited by Sir Cecil Wakeley, K.B.E., C.B., LL.D., M.Ch., D.Sc., F.R.C.S., F.R.S.A., F.R.A.C.S., fellow of King's College, London, senior surgeon, King's College Hospital, director of surgical studies and lecturer in surgery, King's College Hospital Medical School, surgeon, Belgrave Hospital for Children and Royal Masonic Hospital, consulting surgeon to the Royal Navy and examiner in surgery to the University of Cambridge. Twenty-first edition. 8°, cloth, 344 pp., with 45 figures. Baltimore: Williams and Wilkins, 1955. $6.00.

Expert Committee on Drugs Liable to Produce Addiction. Fifth report. 8°, paper, 16 pp., with 2 tables. Geneva: World Health Organization, 1955. $0.30. (No. 95, *World Health Organization Technical Report Series.*)

Cold Injury: Transactions of the third conference February 22, 23, 24 and 25, 1954, Fort Churchill, Manitoba, Canada. Edited by M. Irené Ferrer, M.D., assistant professor of clinical medicine, Columbia University College of Physicians and Surgeons. 8°, cloth, 226 pp., with 31 illustrations and 47 tables. New York: Josiah Macy, Jr., Foundation, 1955. $4.50.

Antisera, Toxoids, Vaccines and Tuberculins in Prophylaxis and Treatment. By H. J. Parish, M.D., F.R.C.P.E., D.P.H., clinical research director, Wellcome Foundation, Limited. Third edition. 8°, cloth, 227 pp., with illustrations. Baltimore: Williams and Wilkins, 1954. $5.00.

Diseases of the Nervous System: Described for practitioners and students. By F. M. R. Walshe, M.D., D.Sc., F.R.S., fellow of the Royal College of Physicians, fellow of University College, London, and consulting physician to University College Hospital and to the National Hospital for Nervous Diseases, Queen Square. Eighth edition. 8°, cloth, 357 pp., with 58 illustrations. Baltimore: Williams and Wilkins, 1955. $7.00.

Experiencing the Patient's Day: A manual for psychiatric hospital personnel. By Robert W. Hyde, M.D., assistant superintendent, Boston Psychopathic Hospital. In collaboration with the attendants of the Boston Psychopathic Hospital. 8°, paper, 214 pp. New York: G. P. Putman's Sons, 1955. $2.20.

The Cortex of the Fifteen-Month Infant. Vol. 5. By J. LeRoy Conel, Ph.D., research associate in pathology, Children's Medical Center. 4°, cloth, 332 pp., with 235 illustrations and 7 tables. Cambridge: Harvard University Press, 1955. $12.50. (*The Postnatal Development of the Human Cerebral Cortex.*)

Reflections on Renal Functions. By James R. Robinson, M.D., Ph.D., (Cantab.), assistant director of research, Department of Experimental Medicine, Medical Research Council and University of Cambridge, and fellow and assistant tutor of Emmanuel College, University of Cambridge. 8°, cloth, 163 pp. Springfield: Charles C Thomas, 1955. $3.50.

Fundamental Considerations in Anesthesia. By Charles L. Burstein, M.D., chief, Department of Anesthesiology, Hospital for Special Surgery, attending consultant in anesthesia, Veterans Administration Hospital, Bronx, New York, and associate clinical professor of anesthesiology, New York University Post-Graduate Medical School. Second edition. 8°, cloth, 219 pp., with 84 illustrations. New York: Macmillan Company, 1955. $5.50.

Annual Review of Medicine. Vol. 6. Edited by David A. Rytand, M.D., Stanford University School of Medicine; and John Anderson, M.D., Stanford University School of Medicine. 8°, cloth, 459 pp., with 3 tables. Stanford: Annual Reviews Incorporated, 1955. $7.00.

Differential Diagnosis of Internal Diseases: Clinical analysis and synthesis of symptoms and signs on pathophysiologic basis. By Julius Bauer, M.D., clinical professor of medicine, College of Medical Evangelists, Los Angeles, senior attending physician, Los Angeles County General Hospital, and consultant in medicine, Long Beach Veterans Administration Hospital. Second edition, revised and enlarged. 8°, cloth, 987 pp., with 66 illustrations and 2 tables. New York: Grune and Stratton, 1955. $15.00.

Airborne Contagion and Air Hygiene: An ecological study of droplet infections. By William Firth Wells. 8°, cloth, 423 pp., with 85 illustrations and 38 tables. Cambridge: Harvard University Press, 1955. $6.00. (Published for the Commonwealth Fund.)

The Casualty Department. By T. G. Lowden, M.A., B.M., B.Ch., F.R.C.S., consultant surgeon, Sunderland Royal Infirmary. 8°, cloth, 278 pp., with 170 illustrations. London: E. and S. Livingstone, Limited, 1955. $7.50. (Distributed in America by Williams and Wilkins, Baltimore.)

Schizophrener Prozess und Schizophrene Symptomgesetze: Eine prognostisch-statistische Grundlagenstudie. By O. H. Arnold, assistant in psychiatric neurology, Universitätsklinik, Wien. 8°, paper, 86 pp., with 16 tables. Vienna: Wilhelm Maudrich, 1955. $3.60. (Distributed in America by Intercontinental Medical Book Corporation, New York City.)

Cytologie des Weiblichen Genitalkarzinoms. By Dr. Edmund Schüller, chief of the laboratory, II. Universitäts-Frauenklinik Wien. With a foreword by Prof. Dr. Hans Zacherl, Wien. 8°, paper, 129 pp., with 66 illustrations and 32 tables. Vienna: Wilhelm Maudrich, 1955. $6.00. (Distributed in America by Intercontinental Medical Book Corporation, New York City.)

Foetal, Infant and Early Childhood Mortality. Vol. 1. *The Statistics.* 4°, paper, 137 pp., with 6 illustrations and 26 tables. $1.50. Vol. 2. *Biological, Social and Economic Factors.* 4°, paper, 44 pp., with 4 illustrations and 54 tables. $0.40. New York: United Nations, 1954. (Distributed by Columbia University Press, New York City.) (No. 13, *Population Studies.*)

Gestation: Transactions of the first conference March 9, 10 and 11, 1954, Princeton, New Jersey. Edited by Louis B. Flexner, M.D., professor of anatomy and chairman, Department of Anatomy, University of Pennsylvania School of Medicine. 8°, cloth, 238 pp., with 97 illustrations. New York: Josiah Macy, Jr., Foundation, 1955. $5.00.

Fluoroscopy in Diagnostic Roentgenology. By Otto Deutschberger, M.D., assistant clinical professor of radiology, New York Medical College, roentgenologist in charge, Bird S. Coler Memorial Hospital, New York City, and associate visiting roentgenologist, Metropolitan Hospital, New York City. With an introduction by Frank J. Borrelli, M.D., professor of radiology, New York Medical College, and director of the departments of Radiology, Flower and Fifth Avenue Hospitals, and Metropolitan Hospital, New York City, and Bird S. Coler Memorial Hospital, New York City. 8°, cloth, 771 pp., with 888 illustrations. Philadelphia: W. B. Saunders Company, 1955. $22.00.

Primary Anatomy. By H. A. Cates, M.B.; and J. V. Basmajian, M.D., associate professor of anatomy, University of Toronto. Third edition. 8°, cloth, 339 pp., with 441 illustrations and 4 plates. Baltimore: Williams and Wilkins, 1955. $6.00.

Antibiotics Annual 1954-1955: Proceedings of the second annual symposium on antibiotics. Edited by Henry Welch, Ph.D.; and Felix Marti-Ibáñez, M.D. 4°, cloth, 1154 pp., with figures and tables. New York: Medical Encyclopedia, Incorporated, 1955. $10.00.

Ionography: Electrophoresis in stabilized media. By Hugh J. McDonald, D.Sc., professor of biochemistry, Stritch School of Medicine of Loyola University, Chicago. In collaboration with Robert J. Lappe, M.S., research assistant, Department of Biochemistry, Loyola University; Edward P. Marbach, Ph.D., associate chemist, American Meat Institute Foundation, and research associate (instructor), Department of Biochemistry, University of Chicago; Robert H. Spitzer, M.S., research assistant, Department of Biochemistry, Loyola University; and Matthew C. Urbin, Ph.D., associate chemist, Chemical Division, Corn Products Refining Company, Argo, Illinois. 8°, cloth, 268 pp., with 29 illustrations and 8 tables. Chicago: Year Book Publishers, Incorporated, 1955. $6.50.

Medical Care for Tomorrow. By Michael M. Davis, Ph.D. 8°, cloth, 497 pp. New York: Harper and Brothers, 1955. $6.50.

The Role of Humoral Agents in Nervous Activity. By Bruno Minz, M.D., research professor, National Center of Scientific Research, Department of General Physiology, Sorbonne, Paris, France. 8°, cloth, 230 pp., with 50 illustrations and 3 tables. Springfield, Illinois: Charles C Thomas, 1955. $7.75. (Publication No. 240, *American Lecture Series.*)

The Hypophyseal Growth Hormone, Nature and Actions. Edited by Richmond W. Smith, Jr., M.D., physician-in-charge, Division of Endocrinology, Henry Ford Hospital, Detroit; Oliver H. Gaebler, M.D., head, Biochemistry Department, Edsel B. Ford Institute for Medical Research, Detroit; and C. N. H. Long, M.D., Sterling Professor of Physiology, Yale University School of Medicine. 8°, cloth, 576 pp., with illustrations and tables. New York: Blakiston Division, McGraw-Hill Book Company, Incorporated, 1955. $12.00. (*International Symposium.*)

Pain: Its mechanisms and neurosurgical control. By James L. White, M.D., chief of neurosurgical service, Massachusetts General Hospital, and associate professor of surgery, Harvard Medical School; and William H. Sweet, M.D., associate visiting neurosurgeon, Massachusetts General Hospital, and associate clinical professor of surgery, Harvard Medical School. With assistance in the psychiatric sections of Chapters 4 and 10 from Stanley Cobb, M.D., Bullard Professor of Neuropathology, emeritus, Harvard Medical School; and Frances J. Bonner, M.D., assistant in psychiatry, Massachusetts General Hospital and Harvard Medical School. 4°, cloth, 736 pp., with 134 illustrations and 53 tables. Springfield, Illinois: Charles C Thomas, 1955. $17.50.

Klinische Elektropathologie. Vol. 1. *Kritische Sammlung elektropathologischer Gutachten aus interner Sicht.* By Dr. med. habil. S. Koeppen, chief physician, Inpatient Department, Stadtkrankenhaus Wolfsburg. Vol. 2. *Die Neurologie des elektrischen Unfalls und des Blitzschlags: Mit einem Kapitel über die elektromagnetischen Wellen und die Atomkräfte.* By Prof. Dr. F. Panse, chief physician, Rheinische Landesklinik für Hirnverletzte, Bonn. 8°, cloth, 424 pp., with 60 illustrations and 3 tables. Stuttgart: Georg Thieme, 1955. $7.85. (Distributed in the United States by the Intercontinental Medical Book Corporation, New York City.)

NOTICES

TUFTS MEDICAL ALUMNI LECTURE

The annual Tufts Medical Alumni lecture will be given by Christopher J. Duncan, M.D., '28, associate chief surgeon, Free Hospital for Women, and clinical associate in gynecology, Harvard Medical School, at Tufts University School of Medicine on Tuesday, January 31, at 4 p.m. The subject will be "The Care of the Female Patient."

HARVARD SCHOOL OF PUBLIC HEALTH SCHOLARSHIP PROGRAM

The Harvard School of Public Health announces that public-health scholarships for the academic year 1956-1957 are available to the following persons who wish to obtain postgraduate education in the field in public health or in one of the basic sciences related to it: physicians; dentists; veterinarians; industrial physicians; public-health nurses with a college degree and satisfactory field experience; social workers with a master's degree from an approved school of social work and acceptable experience in the field of medical or psychiatric social work; health educators with a college degree, training either in health education or in natural and social sciences and experience in general education or community health work; dietitians with a college degree and satisfactory field experience; and college graduates who have concentrated in one of the natural sciences or in engineering (environmental aspects) — for example, biologists, biochemists, nutritionists, microbiologists, parasitologists and biostatisticians.

Applicants must be eligible for admission as a candidate for one of the following degrees: master of public health, doctor of public health, master of science in hygiene, doctor of science in hygiene and master of industrial health.

Further information may be obtained from the Secretary, Harvard School of Public Health, 55 Shattuck Street, Boston 15, Massachusetts.

FIRST REGIONAL STANDARD NOMENCLATURE INSTITUTE

The American Medical Association announces that its first regional Standard Nomenclature Institute will be held at the Hotel Dennis, Atlantic City, New Jersey, February 6-8. The three-day course will offer instructions on the best way of utilizing the *Standard Nomenclature of Diseases and Operations* in the hospital, doctor's office or clinic. Registration will be limited to the first 100 applicants and will not be restricted to registered medical-record librarians. The tuition is free. Applications should be sent to Mrs. Hayden, American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 30–FEBRUARY 8, MARCH 19–28 and JUNE 4–13. Army Medical Service Postgraduate Course. Page 84, issue of July 14.

JANUARY 31. Tufts Medical Alumni Lecture. Page 191.

FEBRUARY 3. Yale University School of Medicine. Yale-New Haven Medical Center. Page 1092, issue of December 15.

FEBRUARY 6, MARCH 5 and APRIL 2. Fried Lecture Series. Page 535, issue of September 22.

FEBRUARY 6–8. First Regional Standard Nomenclature Institute. Notice above.

FEBRUARY 13–16. American College of Surgeons. Page 1136, issue of December 22.

FEBRUARY 14. Harvard Medical Society. Page 44, issue of January 5.

FEBRUARY 15, MARCH 28 and APRIL 18. Greater Boston Medical Society. Page 208, issue of August 4.

FEBRUARY 20–22. Atlanta Graduate Medical Assembly. Page 1136, issue of December 22.

FEBRUARY 29, MARCH 21 and APRIL 25. Massachusetts Heart Association. Page 623, issue of October 6.

MARCH 15–17. American Orthopsychiatric Association. Page 86, issue of January 12.

MARCH 19–22. American Academy of General Practice. Page 1092, issue of December 15.

MARCH 21 and APRIL 26. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.

MARCH 24 and 25. American Psychosomatic Society. Page 260, issue of August 11.

APRIL 3. Third Microcirculatory Conference. Page 139, issue of January 19.

APRIL 23–26. International Academy of Proctology. Page 86, issue of January 12.

MAY 2. Postgraduate Medical Institute. Page 487, issue of September 15.

MAY 3–5. American Goiter Association. Page 348, issue of August 25.

MAY 28–JUNE 1. European Symposium on Vitamin B. Page 578, issue of September 29.

JUNE 21–23. Society of Nuclear Medicine. Page 1092, issue of December 15.

JUNE 21–24. American Academy of Dental Medicine. Page 994, issue of December 1.

AUGUST 19–23. American College of Chest Physicians. Page 840, issue of November 10.

SEPTEMBER 10–14. American Dietetic Association. Page 1180, issue of December 29.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 2

THURSDAY, FEBRUARY 2

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*11:15 a.m. Thoracic Conference. Auricular Function and Digitalis. Dr. Bernard Lown. Main Amphitheater, Peter Bent Brigham Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Staff Conference. Dr. Raymond D. Adams. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.
*8:00 p.m. The Medical Background for the Routine Chest X-Ray of Admission to the General Hospital. Dr. Theodore L. Badger. Nurses' Home. New England Hospital. Columbus and Dimock Street, Boston (Roxbury).

FRIDAY, FEBRUARY 3

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*1:00–3:00 p.m. Combined Medical-Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, FEBRUARY 4

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Benjamin Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference (Blood Clinic). Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, FEBRUARY 6

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.

(Concluded on page xxvi)